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(54) Title: USE OF BHAP COMPOUNDS IN COMBINATION WITH OTHER NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS FOR THE TREATMENT OF HIV INFECTION

(57) Abstract

The present invention are methods of treating a HIV positive human which comprises (1) administering to the HIV positive individual a sensitizingly effective amount of a SENSITIZING HIV-1 INHIBITOR until increased sensitivity to a NON-NUCLEOSIDE HIV TREATMENT DRUG develops, (2) administering to the HIV positive individual an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG. An alternative method is a method of treating a HIV positive human which comprises administering to the HIV positive individual a sensitizingly effective amount of one or more SENSITIZING HIV-1 INHIBITOR concurrently with an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG.

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USE OF BHAP COMPOUNDS IN COMBINATION WITH OTHER NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS FOR THE TREATMENT OF HIV INFECTION

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a method of treating HIV-1 positive individuals with a SENSITIZING HIV-1 INHIBITOR prior to, currently or intermittently with drugs for the treatment of HIV (NON-NUCLEOSIDE HIV TREATMENT DRUG).

2. Description of the Related Art

European Patent Publication Nos. 484 071 A2, 462,800 A2, 462,808 A2, US Patent 5,124,327, 481,802 A1 and Antimicrobial Agents and Chemotherapy 36, 1019 (1992) [MERCK] disclose a variety of pyridinone derivatives useful in the treatment of HIV-1 infection alone or in combination with other anti-virals.

European Patent Publication Nos. 393 529 A1, 393 530 A1, 393,604 A2, 410 148 A1, 415 304 A2, 429 987 A2, 498 290 A1 disclose dipyridodiazepinone derivatives including nevirapine (BI-RG-587) 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one of Boehringer Ingelheim [BOEHRINGER] are useful for in the treatment of HIV-1 infection alone or in combination with other anti-virals.

International Publications Nos. WO 92/00952 and WO 92/00979, and European Patent Publication Nos. 417 840 A1, 0384 522 A1, 336,466 A1, 430 334 A1 of Janssen [JANSSEN] discloses various compounds which are useful in the treatment of HIV-1 infection alone or in combination with other anti-virals. These compounds include (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione, (+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione, (-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide, (-)-α-[(5-methyl-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide, (-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide, (-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzene-acetamide, α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide, α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide, α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide.

A major problem in treating HIV infected individuals with nucleoside and non-nucleoside compounds is that virus resistant to the compounds used for the treatment emerges, see *J. Virol.*, 65, 4887 (1991) and *Proc. Natl. Acad. Sci.*, (USA) 88, 11241 (1991).

The concept of HIV resistance altering the sensitivity to other drugs within the same chemical class has been reported, *Science* 353, 1557 (1991).

Virology 190, 269 (1992) discusses the antiviral properties of three BHAP compounds and the development of drug-resistant viruses. Further, the article discussed the mutations in the

RT gene which leads to amino acid changes in the reverse transcriptase of the resistant strains.

Bioorganic & Medicinal Chemistry Letters 2(12), 1745 (1992) disclosed various nevirapine-like compounds including various imidazo[2',3':6,5]dipyrido[3,2-b:2',3'-e]-1,4-diazepines which are HIV-1 reverse transcriptase inhibitors with greater enzyme affinity than nevirapine.

The present invention is a method of treating HIV infected individuals which increases the sensitivity of the HIV virus to treatment with various non-nucleoside drugs.

SUMMARY OF INVENTION

Dislcosed is a method of treating a HIV positive human which comprises

(1) administering to the HIV positive individual a sensitizingly effective amount of a SENSITIZING HIV-1 INHIBITOR until increased sensitivity to a NON-NUCLEOSIDE HIV TREATMENT DRUG develops,

(2) administering to the HIV positive individual an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG.

Also disclosed is a method of treating a HIV positive human which comprises administering to the HIV positive individual a sensitizingly effective amount of one or more SENSITIZING HIV-1 INHIBITOR concurrently with an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG.

Further disclosed is a NON-NUCLEOSIDE HIV TREATMENT DRUG to prepare a medicament for treatment of HIV positive individuals having strains of HIV showing increased sensivity thereto due to the administration of a SENSITIZING HIV-1 INHIBITOR. Additionally, disclosed is the use of a NON-NUCLEOSIDE HIV TREATMENT DRUG to prepare a medicament for the treatment of HIV positive individuals concurrently receiving a SENSITIZING HIV-1 INHIBITOR.

DETAILED DESCRIPTION OF THE INVENTION

Various nucleoside (AZT) and non-nucleoside reverse transcriptase inhibitors are known as being useful for the treatment of HIV infected individuals. With regard to the non-nucleoside reverse transcriptase inhibitors, see for example, European Patent Publication Nos. 484 071 A2, 462,800 A2, 462,808 A2, 481,802 A1, 393 529 A1, 393 530 A1, 393,604 A2, 410 148 A1, 415 304 A2, 429 987 A2, 498 290 A1, 417 840 A1, 0384 522 A1, 336,466 A1, 430 334 A1, US Patent 5,124,327, International Publications Nos. WO 91/09849, WO 92/00952 and WO 92/00979 and *Antimicrobial Agents and Chemotherapy*, 36, 1019 (1992).

With the NON-NUCLEOSIDE HIV TREATMENT DRUGs, it has become apparent that resistance to the pharmaceutical agent rapidly develops reducing or eliminating the efficacy of NON-NUCLEOSIDE HIV TREATMENT DRUGs.

The SENSITIZING HIV-1 INHIBITOR compounds of the present invention sensitize

the HIV infected individual's HIV to treatment with a NON-NUCLEOSIDE HIV TREATMENT DRUG. It is preferred that the SENSITIZING HIV-1 INHIBITOR, be a BHAP COMPOUND but other HIV-1 RT inhibitors which sensitize HIV infected individuals to treatment with NON-NUCLEOSIDE HIV TREATMENT DRUGs are operable. The BHAP COMPOUNDS are known, see International Publication WO 91/09849. It is preferred that the SENSITIZING HIV-1 INHIBITOR compound be 1-[2-(5-methoxyindolyl)carbonyl]-4-[3-(N-ethylamino)-2-pyridinyl)piperazine (WO 91/09849, EXAMPLE 16) or 1-[2-(5-methanesulfonamidoindolyl)-carbonyl]-4-[3-(N-isopropylamino)-2-pyridinyl]piperazine (WO 91/09849, EXAMPLE 105).

The NON-NUCLEOSIDE HIV TREATMENT DRUGs include the MERCK COMPOUNDS, BOEHRINGER COMPOUNDS and JANSSEN COMPOUNDS, PFIZER COMPOUNDS, but other non-nucleoside HIV-1 reverse transcriptase inhibitors are also operable.

It is preferred that the MERCK COMPOUNDS be selected from the group consisting of

3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-{[(4,7-dimethyl-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one,

5-ethyl-6-methyl-3-(2-phthalimidoethyl)pyridin-2(1H)-one and

3-{[1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-pyridin-2(1H)-one.

It is preferred that the BOEHRINGER COMPOUND be 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one.

It is preferred that the JANSSEN COMPOUNDS be selected from the group consisting of

(+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione,

(+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione,

(-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(5-methyl-2nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide. It is more preferred that the JANSSEN COMPOUND be selected from the group consisting of

(-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(5-methyl-2nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide,

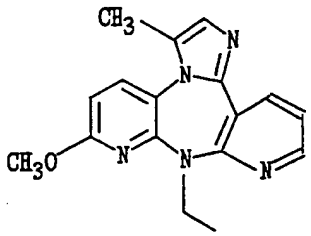
(-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide.

It is preferred that the PFIZER COMPOUND be



There are a number of ways the sensitizing process of the present invention can be used to treat HIV infected individuals (both asymptomatic and those with AIDS). One method involves treating the HIV infected individual with a SENSITIZING HIV-1 INHIBITOR followed by treatment with a NON-NUCLEOSIDE HIV TREATMENT DRUG. Another method involves concurrent administration of the SENSITIZING HIV-1 INHIBITOR and NON-NUCLEOSIDE HIV TREATMENT DRUG.

The first method involves treating the HIV infected individual with a SENSITIZING HIV-1 INHIBITOR followed by treatment with the NON-NUCLEOSIDE HIV TREATMENT DRUG. Using this method the HIV infected individual is given a sensitizingly effective amount of one or more SENSITIZING HIV-1 INHIBITORs until increased sensitivity to a NON-NUCLEOSIDE HIV TREATMENT DRUG develops. This is then followed by administering to the HIV positive individual of an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG. The increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG can be determined clinically and/or *in vitro*. Utilizing the clinical method, the HIV positive individual will have increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG when resistance develops to the SENSITIZING HIV-1 INHIBITOR. Hence, when the clinician notices resistance developing to the SENSITIZING HIV-1 INHIBITOR, the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG will have

occurred and the administration of the SENSITIZING HIV-1 INHIBITOR can be stopped and the administration of the NON-NUCLEOSIDE HIV TREATMENT DRUG can be started.

Alternatively, the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG can be measured *in vitro* by measuring the level of p24 antigen as determined by enzyme-linked immunosorbent assay (ELISA) using any of the number of commercially available ELISA kits. When administration of the SENSITIZING HIV-1 INHIBITOR begins, the level of p24 will decrease. When the level of p24 no longer decreases but begins to increase, the HIV positive individual has become resistant to the SENSITIZING HIV-1 INHIBITOR and has increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG.

An alternative method of determining the HIV positive individual's increased sensitivity is by checking the HIV positive individual's reverse transcriptase for a mutation in the region known to confer resistance to the SENSITIZING HIV-1 INHIBITOR and increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG. If a mutation from proline to leucine occurs at amino acid 236 of the HIV-1 reverse transcriptase, then that individual will have increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG. It is also likely that other mutations in this region of reverse transcriptase, for example changes at the amino acid from about 200 to about 275, more particularly at 233, 234 or 238, will confer resistance to the SENSITIZING HIV-1 INHIBITOR and sensitization to the NON-NUCLEOSIDE HIV TREATMENT DRUG. These changes can be monitored or detected by means known to those skilled in the art, see for example *J. Virol.*, 65, 4887 (1991); *Proc. Natl. Acad. Sci. (USA)* 88,11241 (1991); *Proc. Natl. Acad. Sci. (USA)* 89, 1934 (1992); *Journ. of Medical Virology*, 37, 241 (1992).

The sensitizingly effective amount is an amount that achieves a sustainable blood level which can either be below the MIC of the HIV virus or above the MIC of the HIV virus. It is preferred that the amount be an amount that exceeds the MIC of the HIV virus since selection of the sensitized strains will occur more quickly if the MIC of the organism is exceeded for most of the day. One skilled in the art knows how to monitor the blood level to determine if the amount given is above or below the MIC of the HIV virus and is able to then give an amount which will provide a sustainable blood level. The SENSITIZING HIV-1 INHIBITOR is administered in a dosage range of

about 50 to about 3,000 mg per day in a single or divided doses, preferably about 600 to about 2,100 mg per day in divided doses. The SENSITIZING HIV-1 INHIBITOR is given for a period of about two to about 16 weeks, preferably about 8 to about 12 weeks before the HIV infected individual is treated with a NON-NUCLEOSIDE HIV TREATMENT DRUG. More preferably, the transition from administration of the SENSITIZING HIV-1 INHIBITOR to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured either clinically and/or *in vitro* as discussed above. For example, if the SENSITIZING HIV-1 INHIBITOR is 1-[2-(5-methoxyindolyl)carbonyl]-4-[3-(N-ethylamino)-2-pyridinyl)piperazine, an HIV infected individual would be treated with a dose of 3-10 mg/kg orally three or four times daily for 8-12 weeks; if the SENSITIZING HIV-1 INHIBITOR is 1-[2-(5-methanesulfonamidoindolyl)carbonyl]-4-[3-(N-isopropylamino)-2-pyridinyl]piperazine, an HIV infected individual could be treated with a dose of about 0.5 to about 5 mg/kg/dose orally two to four times daily, this would be followed by a NON-NUCLEOSIDE HIV TREATMENT DRUG. Following treatment with SENSITIZING HIV-1 INHIBITOR, the sensitized strains would then be more sensitive to the NON-NUCLEOSIDE HIV TREATMENT DRUG.

The dosages of the NON-NUCLEOSIDE HIV TREATMENT DRUG are known to those skilled in the art. The dosage range is from about 50 to about 4,000 mg per day in either a single or divided doses depending on the particular compounds, preferably from about about 50 to about 2,000 mg. If the NON-NUCLEOSIDE HIV TREATMENT DRUG is a MERCK COMPOUND, it is preferably administered orally in a dosage range of from about 50 to about 2,000 mg, more preferably from about 200 to about 800 mg, one to three times daily. If the NON-NUCLEOSIDE HIV TREATMENT DRUG is a BOEHRINGER COMPOUND, it is preferably administered orally in a dosage range of from about 50 to about 2,000 mg, more preferably from about 50 to about 500 mg per day in a single or divided doses, still more preferably from about 100 to about 200 mg per day as a single dose. If the NON-NUCLEOSIDE HIV TREATMENT DRUG is a JANSSEN COMPOUND it is preferably administered from about 50 to about 2,000 mg, more preferably from about 100 to about 2,000 mg per day either orally in divided doses or by continuous IV infusion depending on the particular compound. More specifically, if the JANSSEN COMPOUND is (+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione, it is administered continuously IV in a total daily

dose of from about 50 to about 1,000 mg daily. More specifically if the JANSSEN COMPOUND is (-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzene- acetamide, it is administered orally in a total daily dose of from about 100 to about 2,000 mg in divided doses two to six times daily. With this method one or more than one SENSITIZING HIV-1 INHIBITOR can be used, likewise one or more than one NON-NUCLEOSIDE HIV TREATMENT DRUG can be used.

This method can involve a multiple of treatment cycles as is known to those skilled in the art. Further, a modified form of this method is after the sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG has increased by the initial administration of the SENSITIZING HIV-1 INHIBITOR, is to administer the SENSITIZING HIV-1 INHIBITOR and NON-NUCLEOSIDE HIV TREATMENT DRUG concurrently rather than terminate the SENSITIZING HIV-1 INHIBITOR. Another alternative form of this method is after the initial administration of the SENSITIZING HIV-1 INHIBITOR to increase the HIV positive individual's sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG, is to administer the SENSITIZING HIV-1 INHIBITOR intermittently with administration of the NON-NUCLEOSIDE HIV TREATMENT DRUG to reduce the probability that the increased sensitivity does not disappear.

The other method of treatment involves initially treating the HIV infected individual with a SENSITIZING HIV-1 INHIBITOR concurrently with the NON-NUCLEOSIDE HIV TREATMENT DRUG. Using this method the HIV infected individual is given both the SENSITIZING HIV-1 INHIBITOR and NON-NUCLEOSIDE HIV TREATMENT DRUG simultaneously. The therapeutic dosage range and frequency of administration of both the SENSITIZING HIV-1 INHIBITOR and NON-NUCLEOSIDE HIV TREATMENT DRUG is the same as for administration of the NON-NUCLEOSIDE HIV TREATMENT DRUG following administration of the SENSITIZING HIV-1 INHIBITOR, the only thing that is different is the sequencing of when the SENSITIZING HIV-1 INHIBITOR and NON-NUCLEOSIDE HIV TREATMENT DRUG are given.

A modification of this process is that after a period of time when increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is obtained, the SENSITIZING HIV-1 INHIBITOR is given intermittently with the NON-NUCLEOSIDE HIV TREATMENT DRUG rather than continuously.

The particular method to be utilized with an particular patient will depend on many factors as will be apparent to those skilled in the art. These factors include whether the patient is symptom free or has some symptoms. Further, if the patient has symptoms are they mild or severe. In addition, other diseases/conditions that affect the patent can enter into the decision as to which method to use in a particular case as is known to those skilled in the art.

The exact dosage and frequency of administration depends on the particular SENSITIZING HIV-1 INHIBITOR and NON-NUCLEOSIDE HIV TREATMENT DRUG used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the SENSITIZING HIV-1 INHIBITOR in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents may be identified by a letter or a letter followed by a numerical subscript, for example, "Z_1" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z_1 would represent a bivalent variable if attached to the formula CH_3-C(=Z_1-)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH_3-CH_2-C(R_i)(R_j)-H. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established

system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term "R_6" represents a variable substituent (either monovalent or bivalent) at the C_6 position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-CH(R_i)-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=C(R_i)-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by N^*=C(CH_3)-CH=CCl-CH=C^*H with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by -N^*-$(CH_2)_2$-N(C_2H_5)-CH_2-C^*H_2.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X_1)(X_2)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta (ß) configuration and is indicated by an unbroken line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or

separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as -C(=R_i)- might be bivalent and be defined as oxo or keto (thus forming a carbonyl group (-CO-) or as two separately attached monovalent variable substituents α-R_{i-j} and ß-R_{i-k}. When a bivalent variable, R_i, is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form "α-R_{i-j}:ß-R_{i-k}" or some variant thereof. In such a case both α-R_{i-j} and ß-R_{i-k} are attached to the carbon atom to give -C(α-R_{i-j})(ß-R_{i-k})-. For example, when the bivalent variable R_6, -C(=R_6)- is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are α-R_{6-1}:ß-R_{6-2}, ... α-R_{6-9}:ß-R_{6-10}, etc, giving -C(α-R_{6-1})(ß-R_{6-2})-, ... -C(α-R_{6-9})(ß-R_{6-10})-, etc. Likewise, for the bivalent variable R_{11}, -C(=R_{11})-, two monovalent variable substituents are α-R_{11-1}:ß-R_{11-2}. For a ring substituent for which separate α and ß orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the α and ß designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula -C_1(R_i)H-C_2(R_j)H- (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group -X-Y-, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form -CH_2-CH_2-O-CO- ..." means a lactone in which the carbonyl is bonded to C_2. However, when designated "... R_j and R_i are taken together to form -CO-O-CH_2-CH_2-the convention means a lactone in which the carbonyl is bonded to C_1.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "C_1-C_4", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given).

Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4 alkoxycarbonyl describes a group CH_3-$(CH_2)_n$-O-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C_i-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C_1-C_3)alkoxycarbonyl has the same meaning as C_2-C_4 alkoxycarbonyl because the "C_1-C_3" refers only to the carbon atom content of the alkoxy group. Similarly while both C_2-C_6 alkoxyalkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

While the above method of defining variable substituents and the number of carbon atoms in various groups is used to define the BHAP COMPOUNDS, it must be realized that there are alternative methods which accomplish the same thing. Admittedly, the specification and claims here are a composite of information obtained electronically from different sources and therefore represents various styles. Never-the-less, one skilled in the art will certainly know what is being disclosed and/or claimed.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

II. DEFINITIONS

All temperatures are in degrees Centigrade.

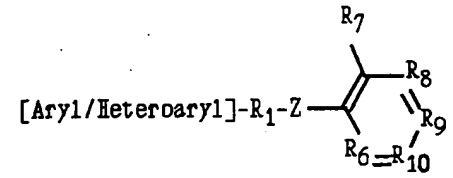
-ϕ refers to phenyl (C_6H_5).

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

MIC refers to minimum inhibitory concentration.

BHAP refers to bisheteroarylpiperazines.

BHAP COMPOUNDS refers to bisheteroarylpiperazines selected from the group consisting of compounds of formula (I)



(I)

where R_1 is $-CH_2-$,

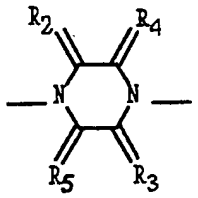
$-CO-$,

$-CO-CH_2-$,

$-SO_2-$,

$-CH=CH-CO-$;

where Z is



(Z-I)

where

(I) R_2 is =O or R_{2-1}:R_{2-2} where one of R_{2-1} and R_{2-2} is -H and the other of R_{2-1} and R_{2-2} is -H or $-CH_3$,

R_3 is =O or R_{3-1}:R_{3-2} where one of R_{3-1} and R_{3-2} is -H and the other of R_{3-1} and R_{3-2} is -H or $-CH_3$,

R_4 is R_{4-1}:R_{4-2} and R_5 is R_{5-1}:R_{5-2} where one of R_{4-1} and R_{4-2} is -H and the other of R_{4-1} and R_{4-2} is -H or $-CH_3$, where one of R_{5-1} and R_{5-2} is -H and the other of R_{5-1} and R_{5-2} is -H or $-CH_3$,

(II) R_4 is R_{4-3}:R_{4-4} and R_5 is R_{5-3}:R_{5-4} where one of R_{4-3} and R_{4-4} and one of R_{5-3} and R_{5-4} are taken together to form $-CH_2-$ and the other of R_{4-3} and R_{4-4}, and R_{5-3} and R_{5-4} are -H, R_2 and R_3 are -H:-H,

(III) R_2 is R_{2-5}:R_{2-6} and R_5 is R_{5-5}:R_{5-6} where one of R_{2-5} and R_{2-6} and one of R_{5-5} and R_{5-6} are taken together to form $-CH_2-CH_2-$ and the other of R_{2-5} and R_{2-6}, and R_{5-5} and R_{5-6} are -H, and R_3 and R_4 are -H:-H,

(IV) R_3 is R_{3-5}:R_{3-6} and R_4 is R_{4-5}:R_{5-6} where one of R_{3-5} and R_{3-6} and one

of R_{4-5} and R_{4-6} are taken together to form $-CH_2-CH_2-$ and the other of R_{3-5} and R_{3-6}, and R_{4-5} and R_{4-6} are -H, and R_2 and R_5 are -H:-H,

$$-Y_1-(CH_2)_{n11}-Z_2-(CH_2)_{n26}-Y_2- \quad \text{(Z-II)}$$

where n_{11} is 1 thru 5,

n_{26} is 1 thru 5,

Y_1 is -O-, -S-,

$-N(Y_{1-1})-$ where Y_{1-1} is C_1-C_4 alkyl,

$-C(Y_{1-2})(Y_{1-3})$ where Y_{1-2} and Y_{1-3} are the same or different and are -H or C_1-C_4 alkyl,

Y_2 is -O-, -S-,

$-N(Y_{2-1})-$ where Y_{2-1} is C_1-C_4 alkyl,

$-C(Y_{2-2})(Y_{2-3})$ where Y_{2-2} and Y_{2-3} are the same or different and are -H or C_1-C_4 alkyl,

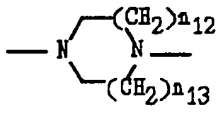
Z_2 is nothing (a bond), -O-, -S-,

$-N(Z_{2-1})-$ where Z_{2-1} is -H or C_1-C_4 alkyl,

$-C\equiv C-$,

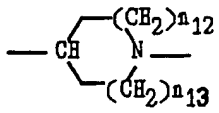
$-C(Z_{2-2})(Z_{2-3})-$ where Z_{2-2} and Z_{2-3} are the same or different and are -H or C_1-C_4 alkyl,

cis and trans $-C(Z_{2-2})=C(Z_{2-3})-$ where Z_{2-2} and Z_{2-3} are the same or different and are -H or C_1-C_4 alkyl, with the provisos (1) that when Y_1 is -O-, -S- or $-N(Y_{1-1})-$, then n_{11} is 1 only when Z_2 is nothing (a bond), $-C\equiv C-$, $-C(Z_{2-2})(Z_{2-3})-$ or $-C(Z_{2-2})=C(Z_{2-3})-$ and (2) that when Y_2 is -O-, -S- or $-N(Y_{2-1})-$, then n_{26} is 1 only when Z_2 is nothing (a bond), $-C\equiv C-$, $-C(Z_{2-2})(Z_{2-3})-$ or $-C(Z_{2-2})=C(Z_{2-3})-$,



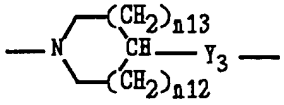
(Z-III)

where n_{12} is 1 or 2 and n_{13} is 1 or 2,



(Z-IV)

where n_{12} and n_{13} are as defined above,



(Z-V)

where Y_3 is $-N(Y_{3-1})-$ where Y_{3-1} is C_1-C_4 alkyl and n_{12} and n_{13} are as defined above;

R_6 is -N=,

-CH=,

-N(O)=,

R_7 is -COO-R_{7-11} where R_{7-11} is as defined above,

-CO-N(R_{7-3})(R_{7-4}) where R_{7-3} and R_{7-4} are the same or different and are -H or C_1-C_6 alkyl,

-N(R_{7-5})(R_{7-6}) where R_{7-5} is

C_1-C_6 alkyl,

-C(R_{7-15})(R_{7-16})-(R_{7-17}) where R_{7-15} and R_{7-16} are the same or different and are -H or C_1-C_3 alkyl and where R_{7-17} is C_2-C_5 alkenyl containing 1 or 2 double bonds or C_2-C_5 alkynyl containing 1 triple bond,

-CH_2-CH_2-OH,

-CH_2-CH_2-CH_2-OH,

-$CH(CH_3)CH_2$-O-CH_3,

-$CH(CH_3)CH_2$-OH,

-CH_2-CF_3,

-CH_2-cyclopropyl,

-CH_2-CH_2F,

-CH_2-CH_2-C≡N,

$-C^*R_{7-18}-(CH_2)_{n14}-C^*H_2$ where R_{7-18} is -H or $-CH_3$, n_{14} is 1 thru 5 and the carbon atoms marked with an asterisk (*) are bonded to each other to resulting in the formation of a ring,

$-(CH_2)n_1-N(R_{7-7})(R_{7-8})$ where n_1 is 2 or 3 and where R_{7-7} and R_{7-8} are the same or different and are -H or C_1-C_4 alkyl, and where R_{7-7} and R_{7-8} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl, 1-aziridinyl,

and where R_{7-6} is -H,

C_1-C_6 alkyl,

$-C(R_{7-15})(R_{7-16})-(R_{7-17})$ where R_{7-15}, R_{7-16} and R_{7-17} are as defined above,

$-CH_2-CH_2-OH$,

$-CH_2-CH_2-CH_2-OH$,

$-CH_2CF_3$,

$-CH_2-CH_2F$,

$-CH_2-CH_2-C\equiv N$,

or where R_{7-5} and R_{7-6} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, N-morpholinyl or 1-aziridinyl,

$-(CH_2)_{n4}-N(R_{7-9})(R_{7-10})$ where n_4 is 1 or 2 and where R_{7-9} and R_{7-10} are the same or different and are -H or C_1-C_4 alkyl, and where R_{7-9} and R_{7-10} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

R_8 is -N=,

$-CR_{8-1}=$ where R_{8-1} is -H, -F, -Cl, -Br, $-CF_3$,

$-NO_2$, $-COCF_3$,

C_1-C_6 alkyl,

C_1-C_3 alkylthio,

-OH,

$-O-R_{8-2}$ where R_{8-2} is C_1-C_6 alkyl, -ϕ, $-CO-R_{8-3}$ where R_{8-3} is C_1-C_6 alkyl or -ϕ,

$-NH(R_{8-4})$ where R_{8-4} is

C_1-C_6 alkyl,

-$C(R_{8-7})(R_{8-8})$-(R_{8-9}) where R_{8-7} and R_{8-8} are the same or different and are -H or C_1-C_3 alkyl and where R_{8-9} is C_2-C_5 alkenyl containing 1 or 2 double bonds or C_2-C_5 alkynyl containing 1 triple bond,

-NR_{8-5}-CO-R_{8-6} where R_{8-5} is -H or C_1-C_6 alkyl and R_{8-6} is -H, C_1-C_6 alkyl or C_1-C_3 alkoxy;

R_9 is -N=,

-CR_{9-1}= where R_{9-1} is -H, -F, -Cl, -Br,

-NO_2, -$COCF_3$,

C_1-C_6 alkyl,

C_1-C_3 alkylthio,

-OH,

-O-R_{9-2} where R_{9-2} is C_1-C_6 alkyl, -ϕ, -CO-R_{9-3} where R_{9-3} is C_1-C_6 alkyl or -ϕ,

-$N(R_{9-4})(R_{9-5})$ where R_{9-4} and R_{9-5} are the same or different and are

-H,

C_1-C_6 alkyl,

-$C(R_{9-8})(R_{9-9})$-(R_{9-10}) where R_{9-8} and R_{9-9} are the same or different and are -H or C_1-C_3 alkyl and where R_{9-10} is C_2-C_5 alkenyl containing 1 or 2 double bonds or C_2-C_5 alkynyl containing 1 triple bond,

R_{9-4} and R_{9-5} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

-NR_{9-6}-CO-R_{9-7} where R_{9-6} is -H or C_1-C_6 alkyl and R_{9-7} is -H, C_1-C_6 alkyl or C_1-C_3 alkoxy;

R_{10} is -N=,

-CR_{10-1}= where R_{10-1} is -H, -F, -Cl, -Br, -CF_3,

-NO_2, -$COCF_3$,

C_1-C_6 alkyl,

C_1-C_3 alkylthio,

-OH,

-O-R_{10-2} where R_{10-2} is C_1-C_6 alkyl, -ϕ, -CO-R_{10-3} where R_{10-3}

is C_1-C_6 alkyl or -ϕ,

-$N(R_{10-4})(R_{10-5})$ where R_{10-4} and R_{10-5} are the same or different and are -H,

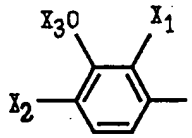
C_1-C_6 alkyl,

-$C(R_{10-8})(R_{10-9})$-(R_{10-10}) where R_{10-8} and R_{10-9} are the same or different and are -H or C_1-C_3 alkyl and where R_{10-10} is C_2-C_5 alkenyl containing 1 or 2 double bonds or C_2-C_5 alkynyl containing 1 triple bond,

-NR_{10-6}-CO-R_{10-7} where R_{10-6} is -H or C_1-C_6 alkyl and R_{10-7} is -H, C_1-C_6 alkyl or C_1-C_3 alkoxy;

with the proviso that not more than two of R_6, R_8, R_9 and R_{10} are -N=;

Aryl/Heteroaryl is a substituent selected from the group of substituents of formula (1)



(1)

where X_1 is -H, C_1-C_6 or n-alkyl,

X_2 is -H, C_1-C_6 or n-alkyl,

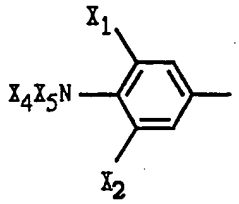
X_3 is C_1-C_6 alkyl,

-CO-X_{3-1} where X_{3-1} is C_1-C_4 alkyl or -ϕ,

-CH_2-ϕ,

-ϕ;

... of formula (2)



(2)

where X_4 and X_5 are the same or different and are -H,

C_1-C_4 alkyl,

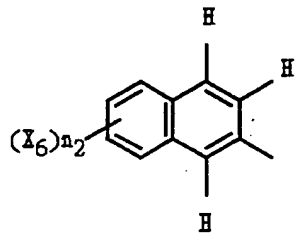
-$(CH_2)_{n5}$-$N(X_{4-1})(X_{4-2})$ where n_5 is 2 or 3 and where X_{4-1} and X_{4-2} are the same or different and are -H or C_1-C_4 alkyl or where X_{4-1} and X_{4-2} are taken

together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

and where X_4 and X_5 are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

and where X_1 and X_2 are as defined above, with the proviso that both X_4 and X_5 are not both -H;

... of formula (3)



(3)

where X_6 is -H,

C_1-C_6 alkyl,

-F, -Cl, Br,

-OH, -O-CH_2-ϕ, -O-CF_3,

-O-CH_2-$COOX_{6-14}$ where X_{6-14} is -H, C_1-C_6 alkyl, -ϕ, -CH_2-ϕ,

-CHO,

C_1-C_3 alkoxy,

C_1-C_3 alkylthio,

-O-CO-X_{6-1} where X_{6-1} is -H, C_1-C_4 alkyl or -ϕ,

-O-SO_2-X_{6-12} where X_{6-12} is C_1-C_4 alkyl,

-COO-X_{6-13} where X_{6-13} is -H, C_1-C_4 alkyl, -ϕ or -CH_2-ϕ,

-C≡N,

-NO_2, -N_3,

-$NX_{6-10}X_{6-11}$ where X_{6-10} and X_{6-11} are the same or different and are

-H or C_1-C_5 alkyl or where X_{6-10} and X_{6-11} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, N-morpholinyl or 1-aziridinyl,

$-N(X_{6-2})(CH_2)_{n3}-N(X_{6-3})(X_{6-4})$ where n_3 is 2 thru 5, X_{6-2} is -H or C_{1-4} alkyl, X_{6-3} is -H or C_{1-4} alkyl, X_{6-4} is -H or C_{1-4} alkyl, or where X_{6-3} and X_{6-4} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, N-morpholinyl or 1-aziridinyl,

$-O-CO-(CH_2)_{n3}-COOH$, where n_3 is as defined above,

$-O-(CH_2)_{n3}-N(X_{6-3})(X_{6-4})$ where n_3, X_{6-3} and X_{6-4} are as defined above,

$-(CH_2)_{n24}-OH$, where n_{24} is 1 thru 5,

$-(CH_2)_{n6}-N(X_{6-5})(X_{6-6})$ where n_6 is 1 thru 5 and X_{6-5} and X_{6-6} are the same or different and are -H, C_1-C_4 alkyl or where X_{6-5} and X_{6-6} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

$-NH-SO_2-X_{6-7}$ where X_{6-7} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, -ϕ or

$-CH_2-\phi$,

$-N=C(X_{6-4})-N(X_{6-7})(X_{6-8})$ where

(a) X_{6-8} is C_1-C_4 alkyl, C_3-C_7 cycloalkyl or -ϕ and where X_{6-4} and X_{6-7} are as defined above,

(b) X_{6-7} and X_{6-8} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

(c) X_{6-4} and X_{6-7} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl or 1-piperidinyl,

$-NX_{6-4}-CO-X_{6-9}$ where X_{6-9} is -H, C_1-C_4 alkyl or -ϕ and where X_{6-4} is as defined above,

-O-prodrug where prodrug is

$-PO_2-O^-$ cation$^+$,

$-CO-CH_2-CO-NH-CH_2-SO_2-O^-$ cation$^+$,

$-CO-(CH_2)_{n21}-R_{51}$ where n_{21} is 1-7 and R_{51} is $-COO^-$ cation$^+$,

$-NR_{51-1}R_{51-2}$ where R_{51-1} and R_{51-2} are the same or different and are -H or C_1-C_3

alkyl,

$-N^{+}R_{51-1}R_{51-2}R_{51-3}$ halide^{-} where R_{51-1}, R_{51-2} and R_{51-3} are the same or different and are

-H or C_1-C_3 alkyl, and where halide is -Cl or -Br,

-CO-CH(amino acid)-NH_2 where amino acid is -H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CH_2-OH$, $-CH(OH)(CH_3)$, $-CH_2-\phi$, $-CH_2$-[p-hydroxyphenyl], $-CH_2$-[3-indolyl], $-CH_2-S-S-CH_2-CH(NH_2)-COOH$, $-CH_2-SH$, $-CH_2CH_2-S-CH_3$, $-CH_2-COOH$, $-CH_2-CO-NH_2$, $-CH_2-CH_2-COOH$, $-CH_2-CH_2-CO-NH_2$, $-CH_2$-[2-HISTIDYL], $-(CH_2)_3-NH-C(NH)-NH_2$, $-(CH_2)_4-NH_2$, $-CH_2-CH_2-CH(OH)-CH_2-NH_2$, $-(CH_2)_3-NH_2$, $-(CH_2)_3-NH-CO-NH_2$ $-CH_2CH_2-OH$,

-CO-CH=CH-CO-O^{-} cation^{+},

$-CO-N^{*}-CH=CH-N=CH^{*}$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring,

$-CO-C^{*}=C[(CH_2)_{n22}-NH_2]-CH=CH-CH=CH^{*}$ where n_{22} is 1 or 2 and where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring,

$-CO-C^{*}=CH-CH=C(-NR_{52})-CH=CH^{*}$ where R_{52} is -H or C_1-C_3 alkyl and where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring,

$-CO-(CH_2)_{n21}-CO-O-[C_6H_{12}O_6$ sugars],

$-CO-O-CH(CH_2-O-CO-R_{53})_2$ where the R_{53}'s are the same or different and are C_1-C_{18},

$-CO-(CH_2)_6-CO-N(CH_3)-CH_2-CH_2-SO_3^{-}$ cation^{+},

$-CH_2-O-CO-(CH_2)_{n21}-NR_{51-1}R_{51-2}$ where n_{21}, R_{51-1} and R_{51-2} are as defined above,

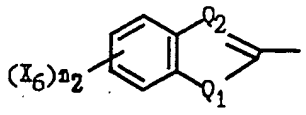
$-CO-NH-C_6H_4-R_{55}$ where R_{55} is -H or C_1-C_3 alkyl, $-NO_2$, $-NR_{51-1}R_{51-2}$ where R_{51-1} and R_{51-2} are as defined above,

$-NX_{6-4}$-prodrug where X_{6-4} and prodrug are as defined above except that prodrug is not $-PO_2-O^{-}$,

n_2 is 1 thru 3, the X_6's can be the same or can be different and where when n_2 is 2 and the two X_6 groups are ortho to each other they can be taken together to form -

$O\text{-}CH_2\text{-}O$-; with the proviso that if n_2 is 2 or 3, only one of the X_6's can be a prodrug,

... of formula (4)



(4)

where Q_1 is $-NX_{11}$- where X_{11} is -H, $-SO_2-\phi$, $-SO_2-CH_3$, $-CO-X_{11-1}$ where X_{11-1} is C_1-C_4 alkyl, $-CF_3$ or $-\phi$;

Q_2 is -N= provided R_1 is not $-CH_2$-,

$-CX_{12}$= where X_{12} is

$-COO-X_{12-1}$ where X_{12-1} is -H or C_1-C_4 alkyl,

$-CO-N(X_{12-2})(X_{12-3})$ where X_{12-2} and X_{12-3} are the same or different and are -H, C_1-C_4 alkyl or where X_{12-2} and X_{12-3} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

$-CO-COO-X_{12-1}$ where X_{12-1} is as defined above,

C_1-C_3 alkyl,

$-CO-\phi$,

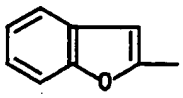
$-CO-X_{12-1}$ where X_{12-1} is as defined above,

$-CO-CO-N(X_{12-2})(X_{12-3})$ where X_{12-2} and X_{12-3} are as defined above,

$-(CH_2)_{n23}$-OH where n_{23} is 1 or 2,

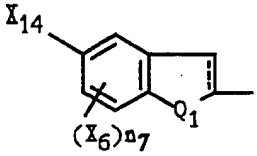
and where X_6 and n_2 are as defined above,

... of formula (6)



(6)

... of formula (7)



(7)

where .... is a single or double bond,

X_{14} is -H,

-O-CH_2-ϕ, -O-CF_3,

-O-CH_2-$COOR_{14-10}$ where R_{14-10} is -H, C_1-C_4 alkyl, -ϕ or -CH_2-ϕ,

C_1-C_6 alkyl,

-F, -Cl, Br,

-O-SO_2-X_{14-11} where X_{14-11} is C_1-C_4 alkyl,

-C≡N,

-CHO,

-$(CH_2)_{n25}$-OH where n_{25} is 1 thru 5,

-NO_2, -NH_2, -N_3,

-NH-CH_2-ϕ, -NH-SO_2-X_{14-1} where X_{14-1} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or -ϕ,

-$NX_{14-2}(CH_2)_{n3}$-$N(X_{14-3})(X_{14-4})$ where n_3 is 2 thru 5, X_{14-2} is -H or C_{1-4} alkyl, X_{14-3} is -H or C_{1-4} alkyl, X_{14-4} is -H or C_{1-4} alkyl, or where X_{14-3} and X_{14-4} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

-$NX_{14-13}X_{14-14}$ where X_{14-13} and X_{14-14} are the same or different and are

-H or C_1-C_5 alkyl or where X_{14-13} and X_{14-14} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

-$(CH_2)_{n6}$-$N(X_{14-5})(X_{14-6})$ where n_6 is 1 thru 5 and X_{14-5} and X_{14-6} are the same or different and are -H, C_1-C_4 alkyl or where X_{14-5} and X_{14-6} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

-N=$C(X_{14-4})$-$N(X_{14-7})(X_{14-8})$ where

(a) X_{14-7} and X_{14-8} are C_1-C_6 alkyl, C_3-C_7 cycloalkyl or -ϕ, where X_{14-4} is as defined above,

(b) X_{14-7} and X_{14-8} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-

piperidinyl, 1-piperazinyl or N-morpholinyl,

(c) X_{14-4} and X_{14-7} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl or 1-piperidinyl,

$-CO-O-X_{14-7}$ where X_{14-7} is as defined above,

$-CO-N(X_{14-7})(X_{14-8})$ where X_{14-7} and X_{14-8} are as defined above,

$-N(X_{14-2})-CO-X_{14-9}$ where X_{14-9} is -H, C_1-C_4 alkyl or -ϕ where X_{14-2} is defined above,

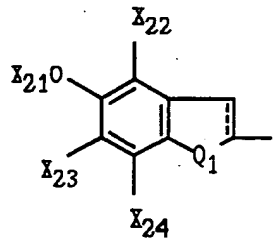
$-N(X_{14-2})$-prodrug, where prodrug is as defined above except that it is not

$-PO_2-O^-$, and when X_{14-2} is as defined above,

n_7 is 0 thru 2,

X_6 and Q_1 are as defined above;

... of formula (8)



(8)

where X_{21} is -H, C_1-C_4 alkyl, -CO-(C_1-C_4 alkyl), $-CH_2-\phi$, -CO-ϕ or -prodrug where prodrug is as defined above,

X_{22}, X_{23} and X_{24} are the same or different and are

-F, -Cl, Br,

-OH, $-O-CH_2-\phi$, $-O-CF_3$, $-O-CH_2-COOH$,

C_1-C_3 alkoxy,

C_1-C_3 alkylthio,

$-O-CO-X_{22-1}$ where X_{22-1} is -H, C_1-C_4 alkyl or -ϕ,

$-NO_2$, $-NH_2$, $-N_3$,

-C≡N,

$-NX_{22-2}(CH_2)_{n9}-N(X_{22-3})(X_{22-4})$ where n_9 is 2 thru 5, X_{22-2} is -H or C_1-C_4 alkyl, X_{22-3} is -H or C_1-C_4 alkyl, X_{22-4} is -H or C_1-C_4 alkyl, and where X_{22-3} and X_{22-4} are taken together with the attached nitrogen atom to form a heterocyclic ring

selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

$-O-CO-(CH_2)_{n9}-COOH$, where n_9 is as defined above,

$-O-(CH_2)_{n9}-N(X_{22-3})(X_{22-4})$ where n_9, X_{22-3} and X_{22-4} are as defined above,

$-(CH_2)_{n10}-N(X_{22-5})(X_{22-6})$ where n_{10} is 1 thru 5 and X_{22-5} and X_{22-6} are the same or different and are -H, C_1-C_4 alkyl and where X_{22-5} and X_{22-6} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl or N-morpholinyl,

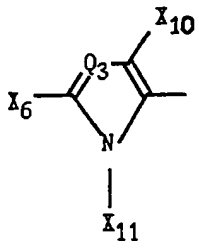
$-N(X_{22-7})(X_{22-8})$ where X_{22-7} and X_{22-8} are C_1-C_6 alkyl, C_3-C_7 cycloalkyl or

-ϕ,

and where any adjacent two of $-O-X_{21}$, X_{22}, X_{23} or X_{24} are taken together to form a methylenedioxy group (-O-CH_2-O-),

Q_1 and .... are as defined above;

... of formula (9)



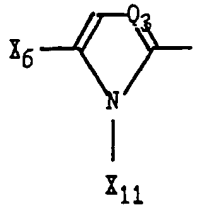
(9)

where X_{10} is -H, -F, -Cl or -Br,

Q_3 is -CH= or Q_2 where Q_2 is as defined above,

X_6 and X_{11} are as defined above;

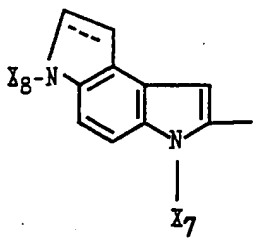
... of formula (10)



(10)

where X_6, X_{11} and Q_3 are as defined above;

... of formula (11)



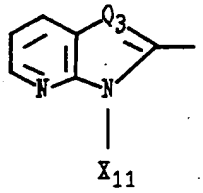
(11)

where X_7 is -H, -SO_2-ϕ, -SO_2-CH_3, -CO-X_{7-1} where X_{7-1} is C_1-C_4 alkyl or -ϕ,

X_8 is -H, C_1-C_6 alkyl, -CH_2-ϕ, -SO_2-ϕ, -SO_2-CH_3, -CO-X_{8-1} where X_{8-1} is C_1-C_4 alkyl or -ϕ,

.... is as defined above;

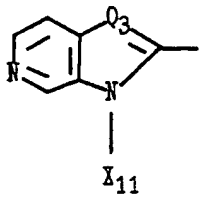
... of formula (15)



(15)

where Q_3 and X_{11} are as defined above;

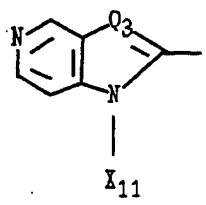
... of formula (16)



(16)

where Q_3 and X_{11} are as defined above;

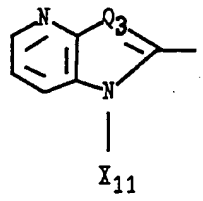
... of formula (17)



(17)

where Q_3 and X_{11} are as defined above;

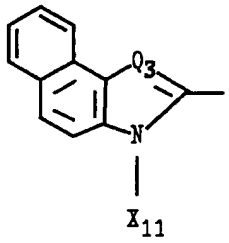
... of formula (18)



(18)

where Q_3 and X_{11} are as defined above;

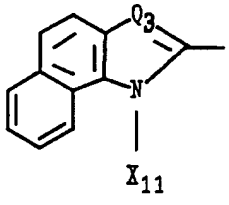
... of formula (19)



(19)

where Q_3 and X_{11} are as defined above;

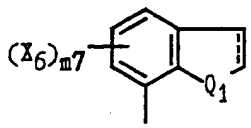
... of formula (20)



(20)

where Q_3 and X_{11} are as defined above;

... of formula (21)



(21)

where Q_1, X_6 and n_7 are as defined above;

with the proviso that one of R_{7-5} or R_{7-6} must be -H when R_6 is not -N=,

enantiomers, pharmaceutically acceptable salts, hydrates and solvates thereof and anti-AIDS piperazines (II) selected from the group consisting of

1-[4-methoxy-3,5-dimethylbenzoyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-[4-methoxy-3,5-dimethylbenzyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-[4-hydroxy-3,5-dimethylbenzyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-[4-methoxy-3,5-dimethylbenzyl]-4-[3-(propylamino)-2-pyridinyl]piperazine,

1-[4-methoxybenzyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-[5-methoxyindolyl-2-carbonyl]-4-[2-ethoxyphenyl]piperazine,

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]-piperazine,

1-[5-methoxyindolyl-2-carbonyl]-4-[2-(ethylamino)phenyl]piperazine,

1-[5-hydroxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-[5-hydroxyindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]piperazine,

1-[5-methoxy-4,6,7-trimethylindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]-piperazine,

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(1,1-dimethylethylamino)-2-pyridinyl]-piperazine,

1-(5-methoxyindolyl-2-carbonyl)-4-[3-(methylamino)-2-pyridinyl]piperazine,

1-[3,5-dimethyl-4-methoxybenzoyl]-4-[3-(ethylamino)-2-phenyl]piperazine,

1-[3,5-dimethyl-4-methoxybenzoyl]-4-[3-(1-methylethylamino)-2-pyridinyl]-piperazine,

1-[5-methoxyindolyl-2-methyl]-4-[3-(ethylamino)-2-pyridinyl]piperazine,

1-(5-fluoroindolyl-2-carbonyl)-4-[3-(1-methylethylamino)-2-pyridinyl]-1,4-diazepine,

N,N'-dimethyl-N-(5-methoxyindolyl-2-carbonyl)-N'-(3-(1-methylethylamino)-2-

pyridyl)ethylenediamine,

1-[4-methoxy-3,4-dimethylbenzyl]-4-(3-(2-propenylamino)-2pyridinyl]piperazine,

N,N′-dimethyl-N-(5-methoxyindolyl-2-carbonyl)-N′-[3-(1-methylethylamino)-2-pyridinyl]-2E-butylenediamine,

N,N′-dimethyl-N-(5-methoxyindolyl-2-carbonyl)-N′-[3-(1-methylethylamino)-2-pyridinyl]-2Z-butylenediamine,

1-(5-methoxyindolyl-2-carbonyl)-4-[3-methylamino-2-pyridinyl]piperazine,

1-(5-methoxyindolyl-2-carbonyl)-4-[3-propylamino-2-pyridinyl]piperzine,

1-(5-methoxyindolyl-2-carbonyl)-4-[3-(cyclo-propylmethylamino)-2-pyridinyl]-piperazine,

1-(5-methoxyindolyl-2-carbonyl)-4-[3-(1,1-dimethylethylamino)-2-pyrazinyl]-piperazine and enantiomers, pharmaceutically acceptable salts, hydrates and solvates thereof.

MERCK 1 refers to the aminopyrimmidones of claim 1 of European Publication 484 071 A2:

3-{[(4,7-dichlorobenzoaxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H-pyridinone,

3-{[(4,7-dimethylbenzoxaxazol-2-yl)methyl]amino}-5-ethyl-6-ethyl-2(1H)-pyridinone,

3-{[(7-chlorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(7-methylbenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4-fluorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(7-fluorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methy-2(1H)-pyridinone,

3-{[(4-chlorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4-fluoro-7-chlorobenzoxazol-2-yl)methyl]lamino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5-ethyl-2-methoxy-6-methyl-3-pyridylmethyl)-amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5,6-dimethyl-2-methoxy-3-pyridylmethyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5-ethyl-2-methoxybenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(2-methoxy-4,5-dimethylbenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(2,6-dimethoxybenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3'-azido-2,3'-dideoxythymidine,

2',3'-dideoxycytidine,

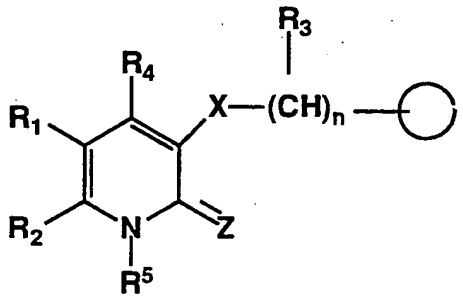
2',3'-dideoxyinosine,

2',3'-didehydro-2',3'-dideoxythymidine,

1[(2-hydroxyethoxy)methyl]-6-phenyl-thiothymine,

3'-fluoro-2',3'-dideoxythymidine or pharmaceutically acceptable salts, hydrates or esters thereof.

MERCK 2 refers to the compounds of claims 1 and 11 of European Publication 462 800 A2, pyridones of the formula:



where X is -NR-, -O-, -S-, -CRH-, -SO-, -SO_2-, -CO-, -CH(OR)-, -CH_2CH(OH)-, -CH_2-CO-, -RC=CR-, -N(-CO-R)-, -N(-CH_2-CO_2R)-, -NR-(SO)-, -NR-(SO_2)-, or -NR-CO-, where R is -H, C_{1-8}alkyl,

Z is 0, S or NR_x is H or C_{1-8} alkyl,

n is 0-4;

R_1, R_2 and R_4 are the same or different and are independently

(i) H;

(ii) C_{1-8} alkyl, C_{1-8} alkenyl, C_{3-8} cycloalkyl, any of which is unsubstituted or substituted with one or two of C_{1-3} alkoxy, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-3} alkylthio, hydroxy, amino, carbonyl, aminocarbonyl, or oximido, or one to five of halo;

(iii) C_{1-6} alkylthio;

(iv) C_{1-5} alkylsulfinyl;

(v) C_{1-5} alkylsulfonyl;

(vi) C_{1-5} alkoxy;

(vii) C_{1-5} alkoxycarbonyl;

(viii) cyano;

(ix) halo; or

(x) aryl;

or R_1 and R_4 may together form a cycloalkyl ring containing 5-7 members;

or R_1 and R_2 may together form a cycloalkyl ring containing 5-7 members;

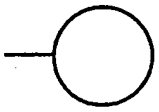
and R_3 or R_5 are the same or different and are independently

(i) H;

(ii) C_{1-8} alkyl;

(iii) C_{1-8} alkenyl;

(iv) C_{3-8} cycloalkyl;



is aryl or heterocycle each unsubstituted or substituted with one or more of

(i) C_{1-6} alkyl unsubstituted or substituted with one or more of A, wherein A is halo, hydroxy, hydroxy-C_{1-4} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkoxy or aryl,

(ii) C_{1-6} alkenyl unsubstituted or substituted with one or more of A;

(iii) C3,6 cycloalkyl unsubstituted or substituted with one or more of A;

(iv) C_{1-6} alkoxy unsubstituted or substituted with one or more or A;

(v) aryl;

(vi) amino,

(vii) C_{1-6} alkylamino;

(viii) di(C_{1-6}-alkyl)amino;

(ix) amino-C_{1-8} alkyl;

(x) C_{1-8} alkyl-amino-C_{1-8} alkyl;

(xi) di-(C_{1-6} alkyl)amino C_{1-8} alkyl;

(xii) C_{1-6} alkoxycarbonyl;

(xiii) aminocarbonyl;

(xiv) C_{1-6} alkyl aminocarbonyl;

(xv) di(C_{1-6} alkyl)aminocarbonyl;

(xvi) C_{1-6} alkylthio;

(xvii) C_{1-6} alkylsulfinyl;

(xviii) C_{1-6} alkylsulfonyl;

(xix) hydroxy;

(xx) halo;

(xxi) CN, or

(xxii) NO_2 with the provisos that

(I) R_1, or R_2 or both are not substituted with OH; and

(II) heterocycle is not phthalimide; or pharmaceutically acceptable salt, hydrate or ester thereof; and the following compounds:

3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4,7-dimethylbenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(7-chlorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(7-methylbenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4-fluorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(7-fluorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(7-fluorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4-chlorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4-fluoro-7-chlorobenzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(4,7-dimethylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(4-methylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(7-methylbenzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5-ethyl-2-methoxy-6-methyl-3-pyridylmethyl)-amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5-(2-hydroxyethyl)-2-methoxy-6-methyl-3-pyridylmethyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5-(1-hydroxyethyl)-2-methoxy-6-methyl-3-pyridylmethyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5,6-dimethyl)-2-methoxy-3-pyridylmethyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(5-ethyl-2-methoxybenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(2-methoxy-4,5-dimethylbenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(2,6-dimethoxybenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]amino}-5-methylthio-6-methyl-2(1H)-pyridinone,

3-{[(4,7-dichlorobenzoxazol-2-yl)methyl]thio}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[N-(2-methoxy-5-methylbenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[(5-ethyl-2-methoxy-6-methyl-3-pyridinylmethyl)-amino]-S-cyclopropyl-6-methyl-2(1H)-pyridinone,

3-[N-(2-methoxy-4-methylbenzyl)amino]-5-ethyl-6-methyl-2(1H)-pyridinone,

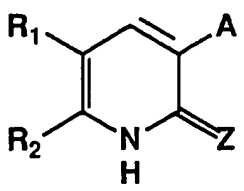
3-{N-[(4,7-dichlorobenzoxazol-2-yl)methyl-N-methyl-amino}-5-ethyl-6-methyl-2(1H)-pyridinone,

3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-propyl-6-methyl-2(1H)-pyridinone,

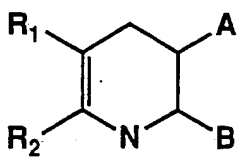
3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-thione,

or, 3-[2-(7-fluorobenzoxazol-2-yl)ethyl]5-ethyl-6-methylpyridin-2(1H)-one or pharmaceutically acceptable ester thereof.

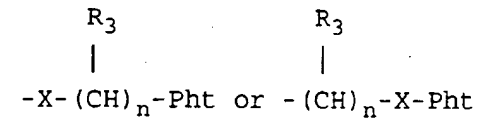
MERCK 3 refers to the compounds of claim 1 of European Publication 462 808 A2, pyridones of the formulae:



or



wherein A is



B is C_{1-6}alkoxy;

X is NH, O, S, or C_2;

Z is O or S;

n is 1-4;

R_1 is

(i) C_{1-8}alkyl, unsubstituted or substituted with one or two of C_{1-3}alkoxy, halo, C_{1-4}alkylamino, C_{1-4}-dialkylamino, or C_{1-3}alkylthio;

(ii) C_{1-3}alkylthio;

(iii) C_{1-3}alkoxy; or

(iv) halo;

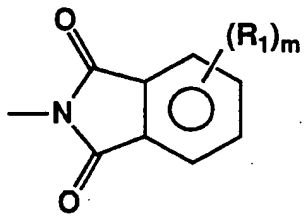
R_2 is

(i) H;

(ii) C_{1-2}alkyl, unsubstituted or substituted with one or two of methoxy, methylamino, dimethylamino or methylthio,

R_3 is H or C_{1-8}alkyl;

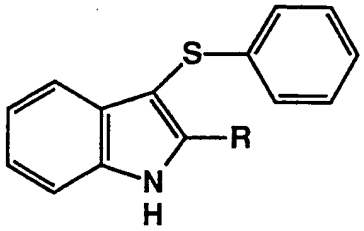
Pht is phthaloyl, of the structure



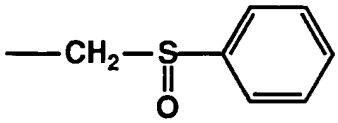
wherein m is 0-2,

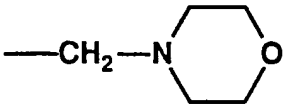
with the proviso that when A is $NHCH_2$-Pht, both R_1 and R_2 cannot be C_{1-2}alkyl.

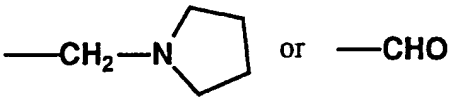
MERCK 4 refers to the compounds of claim 1 of US Patent 5,124,327, indoles of the formula:



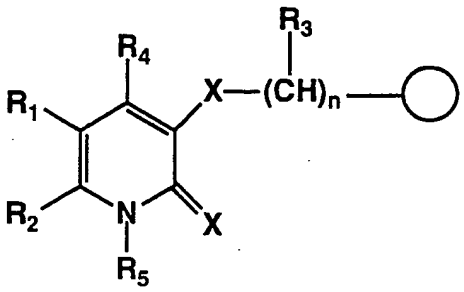
wherein R is







MERCK 5 refers to the compounds of claim 1 of European Publication 481 802 A1, hydroxy pyridinones of the formula:



where R_1 or R_2 or both are substituted at least once with OH;

where X is -NR-, -O-, -S-, -CRH-, -SO-, -SO_2-, -CO-, -CH(OR)-, -CH_2CH(OH)-, -CH_2-CO-, -RC=CR-, -N(-CO-R)-, -N(-CH_2-CO_2R)-, -NR-(SO)-, -NR-(SO_2)-, or -NR-CO-, where

R is H, C_{1-8} alkyl, C_{1-8} alkenyl or C_{3-8} cycloalkyl;

Z is 0, S or NR_x when R_x is H or C_{1-8} alkyl;

n is 0-4;

R_1, R_2 and R_4 are the same or different and are independently

(i) H;

(ii) C_{1-8} alkyl, C_{1-8} alkenyl, C_{3-8} cycloalkyl; any of which is unsubstituted or substituted with one or two of C_{1-3} alkoxy, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-3} alkylthio, hydroxy, amino, oxo, carbonyl, aminocarbonyl, or oximido, or one to five of halo;

(iii) C_{1-5} alkylthio;

(iv) C_{1-5} alkylsulfinyl;

(v) C_{1-5} alkylsulfonyl;

(vi) C_{1-5} alkoxy;

(vii) C_{1-5} alkoxycarbonyl;

(viii cyano; or

(ix) aryl; or,

R_1 and R_4 may together form a cycloalkyl ring containing 5-7 members; or,

R_1 and R_2 may together form a cycloalkyl ring containing 5-7 members; and

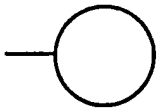
R_3 or R_5 are the same or different and are independently

(i) H;

(ii) C_{1-8} alkyl;

(iii) C_{1-8} alkenyl;

(iv) C_{3-8} cycloalkyl;



is aryl or heterocycle, each unsubstituted or substituted with one or more of

(i) C_{1-6} alkyl unsubstituted or substituted with one or more of A, wherein A is halo, hydroxy, hydroxy-C_{1-4} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6}alkyl)amino or aryl;

(ii) C_{1-6} alkenyl unsubstituted or substituted with one or more of A;

(iii) C_{3-6} cycloalkyl unsubstituted or substituted with one or more of A;

(iv) C_{1-6} alkoxy unsubstituted or substituted with one or more of A;

(v) aryl;

(vi) amino;

(vii) C_{1-6} alkylamino

(viii) di(C_{1-6} alkyl)amino;

(ix) amino-C_{1-8} alkyl;

(x) C_{1-8} alkyl-amino-C_{1-8} alkyl;

(xi) di(C_{1-6} alkyl)amino C_{1-8} alkyl;

(xii) C_{1-6} alkoxycarbonyl;

(xiii) aminocarbonyl;

(xiv) C_{1-6} alkyl aminocarbonyl;

(xv) di(C_{1-6} alkyl aminocarbonyl;

(xvi) C_{1-6} alkylthio;

(xvii) C_{1-6} alkylsulfinyl;

(xviii) C_{1-6} alkylsulfonyl;

(xix) hydroxy;

(xx) halo;

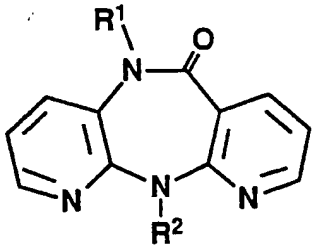
(xxi) CN; or

(xxii) NO_2; with the proviso that heterocycle is not phthalimide; or pharmaceutically acceptable salt or ester thereof.

MERCK 6 refers to the compound of *Antimicrobial Agents and Chemotherapy* 36, 1019 (1992), 3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one.

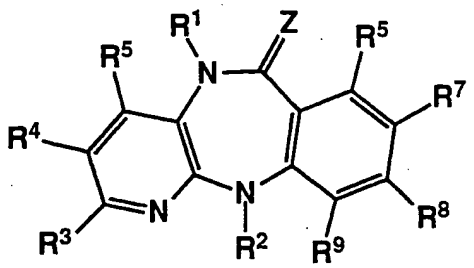
MERCK COMPOUNDS refers to the compounds of MERCK 1, MERCK 2, MERCK 3, ... MERCK 6.

BOEHRINGER 1 refers to the compounds of claim 1 of European Publication 393 529 A1, 5,11-dihydro-6H-dipyrido[3,2-b:2'.3'-e][1,4]diazepin-6-ones of the formula:



where R^1 and R^2 are the same or different and are hydrogen or straight or brtanched alkyl of 1 to 5 carbon atoms, or a pharmaceutically acceptable acid addition salt thereof.

BOEHRINGER 2 refers to the compounds of claim 1 of European Publication 393 530 A1, 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-ones and -thiones of the formula:



wherein,

Z is oxygen or sulfur:

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 4 carbon atoms, cyclopropyl, alkenyl or alkynyl of 3 to 4 carbon atoms, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl or thienyl, which is either unsubstituted or substituted by methyl, methoxy or halogen), acetyl, or alkoxyalkyl or alkylthioalkyl of 2 to 3 carbon atoms;

R^2 is alkyl or fluoroalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 5 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 3 carbon atoms, alkanoyl of 2 to 3 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), phenyl (which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, halogen or hydroxyl) or alkoxy carbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms:

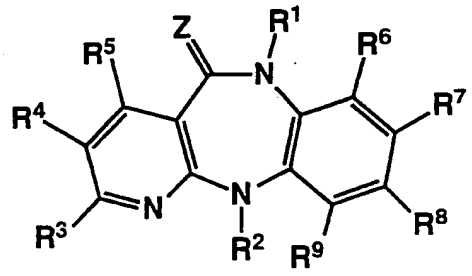
R^3, R^4 and R^5 are each independently hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that at least one of these substituents is hydrogen; or one of R^3, R^4 and R^5 is butyl, alkanoyl of 2 to 4 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, halogen, trihalomethyl, hydroxyl, alkoxy of 1 to 3 carbon atoms, alkylthio of 1 to 3 carbon atoms, alkanoyloxy of 2 to 3 carbon atoms, alkanoylamino of 1 to 3 carbon atoms, aminoalkyl of 1 to 3 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, carboxyalkyl of 2 to 3 carbon atoms, cyano, nitro, carboxyl, carbamyl, amino, azido, mono- or dialkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, with the proviso that the remaining two substituents are hydrogen or methyl; or,

when Z is oxygen, one of R^3, R^4 and R^5 is alkylsulfinyl or alkylsulfonyl of 1 to 3 carbon atoms with the proviso that the remaining two substituents are hydrogen or methyl; and

R^6, R^7, R^8 and R^9 are hydrogen; or

one of R^6, R^7, R^8 and R^9 is alkyl of 1 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, halogen, trihalomethyl, hydroxyl, alkoxy of 1 to 3 carbon atoms, alkylthio of 1 to 3 carbon atoms, alkanoyloxy of 2 to 3 carbon atoms, alkanoylamino of 1 to 3 carbon atoms,aminoalkyl of 1 to 3 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, carboxyalkyl of 2 to 3 carbon atoms, cyano, nitro, carboxyl, carbamyl, amino, azido, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, and the remaining three substituents are hydrogen or two of the remaining three substituents are hydrogen and one is methyl, ethyl or halogen, or a pharmaceutically acceptable acid addition salt thereof.

BOEHRINGER 3 refers to the compounds of claim 1 of European Publication 393,604 A2, 6,11-dihydro-5H-pyrido[2,3-b][1,5]benzodiazepin-5-ones and -thiones of the formula:



wherein,

Z is oxygen or sulfur;

R^1 is hydrogen, alkyl or fluoroalkyl of 1 to 5 carbon atoms, cyclopropyl, alkenyl or alkynyl of 3 to 5 carbon atoms, 2-halo-propen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubsbtuted or substituted by methyl, methoxy or halogen), alkanoyl of 2 to 3 carbon atoms, or alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms:

R^2 is alkyl or fluoroalkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms, alkenyl or alkynyl of 2 to 5 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, hydroxyalkyl of 2 to 5 carbon atoms, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms,

hydroxyl, or halogen), phenyl (which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, halogen or hydroxyl) or alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms;

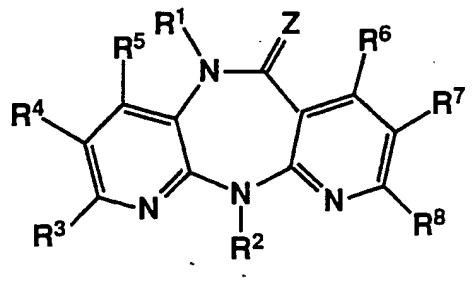
R^3, R^4, and R^5 are each independently hydrogen or alkyl of 1 to 3 carbon atoms, with the proviso that at least one of these substituents is hydrogen; or, one of R^3, R^4 and R^5 is butyl, alkanoyl of 1 to 3 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkoxycarbonyl of 2 to 3 carbon atoms, alkoxycarbonylalkyl wherein both the alkoxy and alkyl moieties contain 1 to 2 carbon atoms, halogen, trihalomethyl, hydroxyl, alkoxy of 1 to 3 carbon atoms, alkythio of 1 to 3 carbon atoms, alkanoyloxy of 2 to 3 carbon atoms, alkanoylamino of 1 to 3 carbon atoms, aminoalkyl of 1 to 3 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, carboxyalkyl of 2 to 3 carbon atoms, cyano, nitro, carboxyl, carbamyl, amino, azido or mono- or dialkylaminoalkyl wherein the alkyl moieties each contain 1 to 2 carbon atoms, and the remaining two substituents are hydrogen or methyl; or,

when Z is oxygen, one of R^3, R^4 and R^5 is alkylsulfinyl or alkylsulfonyl of 1 to 3 carbon atoms, with the proviso that the remaining two substituents are hydrogrogen or methyl; and,

R^6, R^7, R^8 and R^9 are each hydrogen; or,

one of R^6, R^7, R^8 and R^9 is alkyl of 1 to 4 carbon atoms, alkanoyl of 1 to 3 carbon atoms, alkoxycarbonyl of 2 to 3 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein both the alkoxy and alkyl moieties contain 1 to 2 carbon atoms, halogen, trihalomethyl, hydroxyl, alkoxy of 1 to 3 carbon atoms, alkylthio of 1 to 3 carbon atoms, alkanoyloxy of 2 to 3 carbon atoms, alkanoylamino of 1 to 3 carbon atoms, aminoalkyl of 1 to 3 carbon atoms, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 2 carbon atoms, carboxyalkyl of 2 to 3 carbon atoms, cyano, nitro, carboxyl, carbamyl, amino, azido or mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, and the remaining three substituents are hydrogen or two of the remaining three substituents are hydrogen and one is methyl, ethyl or halogen; or a pharmaceutically acceptable acid addition salt thereof.

BOEHRINGER 4 refers to the compounds of claim 1 of European Publication 410 148 A1, 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-ones and -thiones of the formula:



wherein,

Z is oxygen or sulphur;

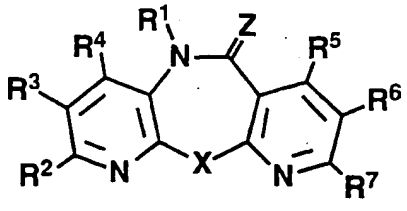
R^1 is hydrogen, C_{1-5}alkyl optionally substituted by fluorine, trihalomethyl, C_{3-5}alkenyl or alkynyl, 2-halopropen-1-yl, arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl and is optionally substituted by methyl, methoxy or halogen), C_{2-3} alkanoyl or C_{2-4} alkoxyalkyl or alkylthioalkyl;

R^2 is hydrogen, C_{1-5} alkyl optionally substituted by fluorine, C_{2-5}alkenyl or alkynyl, C_{2-4} alkoxyalkyl or alkylt hioalkyl, C_{2-4}alkanoyl, C_{2-5}hydroxyalkyl, arylmethyl (where in the aryl moiety is phenyl, thienyl or furanyl, and is optionally substituted by C_{1-3} alkyl or alkoxy, hydroxyl or halogen), phenyl optionally substituted by C_{1-3} alkyl or alkoxy groups, hydroxy or halogen or (C_{1-5}alkoxy)carbonylmethyl; and

R^3, R^4, R^5, R^6, R^7 and R^8 is each hydrogen, or one of R^3, R^4, R^5, R^6, R^7 and R^8 is an alkyl, alkoxy, alkylthio, alkoxycarbonyl, hydroxyalkyl, alkanoyl, alkanoyloxy, alkanoylamino, carboxyalkyl or aminoalkyl group containing up to 4 carbon atoms, or a (C_{1-2}alkoxy)carbonyl(C_{1-2}alkyl), mono- or di-(C_{1-2}alkyl)amino, cyano, nitro, hydroxyl, carboxyl, amino, mono- or di-(C_{1-2}alkyl)amino(C_{1-2}alkyl) or azido group or a halogen atom and the remaining five of R^3, R^4, R^5, R^6, R^7 and R^8 are each hydrogen, or

R^3, R^4 and R^5, are each independently hydrogen or C_{1-3}alkyl with the proviso that at least one is hydrogen, or one of R^3, R^4 and R^5 is butyl with the remaining two being hydrogen, and R^6, R^7 and R^8 are each independently hydrogen or C_{1-3}alkyl with the proviso that at least one is hydrogen, or one of R^6, R^7 and R^8 is butyl with the remaining two being hydrogen; with the proviso that when R^1 and R^2 are each independently hydrogen or straight-chained or branched C_{1-5}alkyl and R^3, R^4, R^5, R^6, R^7 and R^8 are all hydrogen then Z is sulphur) or an acid addition salts thereof.

BOEHRINGER 5 refers to the compounds of claim 1 of European Publication 415 304 A2, dipyrido[3,2-b:2',3'-e][1,4]oxazepin (and thiazepin)-6(5H)-ones and -thiones of the formula:



wherein,

X is oxygen or sulfur;

Z is oxygen or sulfur;

R^1 is alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms, fluoroalkylmethyl of 1 to 3 fluorine atoms and 2 to 4 carbon atoms, mono- or dihaloalkenyl of 2 to 4 carbon atoms wherein the halogen atoms are attached to the vinylic carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, alkyloxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, aminocarbonylmethyl, acetyl, cyanoalkyl and wherein the alkyl moiety contains 1 to 3 carbon atoms, or hydroxyalkylmethyl of 2 to 4 carbon atoms;

R^2 is hydrogen, methyl, ethyl, halogen, nitro or amino;

R^3 is hydrogen, methyl, or halogen;

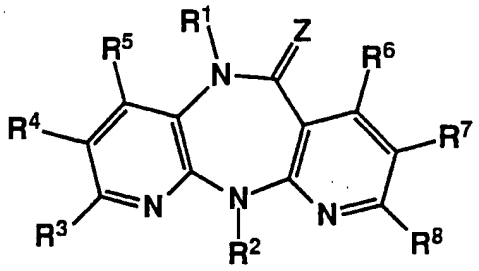
R^4 is hydrogen, alkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 3 carbon atoms, trihalomethyl, alkanoyl of 2 to 3 carbon atoms, cyano azido, amino, nitro, halogen, hydroxyl, alkyloxy or alkylthio of 1 to 2 carbon atoms, mono or di-alkylamino wherein each alkyl group contains 1 to 2 carbon atoms, aminoalkyl or mono- or di-alkylaminoalkyl wherein each alkyl group contains 1 to 2 carbon atoms, hydroxyalkyl of 1 to 3 carbon atoms or alkyloxycarbonyl of 2 to 3 carbon atoms; with the proviso that when R^4 is other than hydrogen, R^2 is hydrogen, methyl or chloro and R^3 is hydrogen;

R^5 is hydrogen, methyl or halogen;

R^6 is hydrogen, methyl, halogen or amino; and

R^7 is hydrogen, methyl or halogen; with the proviso that at least two of R^5, R^6 and R^7 is hydrogen, or a pharmaceutically acceptable salt thereof.

BOEHRINGER 6 refers to the compounds of claim 1 of European Publication 429 987 A2, 5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepines of the formula:



wherein,

Z is oxygen, sulfur, = NCN, or a group of the formula = NOR^9 wherein R^9 is alkyl of 1 to 3 carbon atoms;

R^1 is hydrogen, alkyl of 1 to 6 carbon atoms, fluoroalkyl of 1 to 6 carbon atoms and 1 to 3 fluorine atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 6 carbon atoms, 2-halo-2-propen-1-yl, mono- or di-halovinyl, aryl or arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by methyl, methoxy or halogen), alkanoyl of 2 to 4 carbon atoms, aminoethyl, mono- or di-alkylaminoethyl wherein each alkyl moiety contains 1 to 2 carbon atoms, alkyloxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkyloxycarbonal wherein the alkyl moiety contains 1 to 4 carbon atoms, alkenyloxy- or alkynyloxycarbonyl wherein each alkenyl or alkynyl moiety contains 2 to 4 carbon atoms, hydroxy, alkyloxy of 1 to 4 carbon atoms, amino, mono- or di-alkylamino wherein each alkyl moiety contains 1 to 4 carbon atoms, aminocarbonylmethyl, or cyanoalkyl wherein the alkyl moiety contains 1 to 4 carbon atoms;

R^2 is hydrogen (with the proviso that R^1 is not hydrogen), alkyl of 1 to 6 carbon atoms, fluoroalkyl of l to 6 carbon atoms, and 1 to 3 fluorine atoms, cycloalkyl of 3 to 6 carbon atoms, oxetanyl, thietanyl, tetrahydrofuranyl or tetrahydrothienyl, alkenyl or alkynyl of 2 to 6 carbon atoms, alkyloxyalkyl or alkylthioalkyl of 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms, cyano, hydroxyalkyl of 2 to 6 carbon atoms, aryl or arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkyloxy of 1 to 3 carbon atoms, hydroxyl or halogen), or alkyloxycarbonylmethyl wherein the alkyl moiety contains 1 to 5 carbon atoms; and,

one of R^3, R^4 and R^5 is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 6 carbon atoms, trihalomethyl hydroxyalkyl of 1 to 6 carbon atoms, alkyloxyalkyl or alkylthioalkyl of 2 to 5 carbon atoms, alkyloxycarbonylalkyl wherein the alkyl moieties each contain 1 to 2 carbon atoms, hydroxyl, alkyloxy or alkylthio of 1 to 5 carbon atoms, hydroxyalkyloxy of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkylsulfinyl or alkylsulfonyl of 1 to 4 carbon atoms, alkanoyl of 2 to 6 carbon atoms, alkyloxycarbonyl wherein the

alkyl moiety contains 1 to 3 carbon atoms, mono- or di-alkylaminocarbonyl wherein each alkyl moiety contains 1 to 3 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 3 carbon atoms, aryl or arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkyloxy of 1 to 3 carbon atoms, hydroxyl or halogen), a group of the formula $-NR^{10}R^{11}$, halogen, cyano, nitro, azido or carboxyl, with the other two substituents being hydrogen, methyl or chloro; or, two of R^3, R^4 and R^5 are independently alkyl or hydroxyalkyl of 1 to 2 carbon atoms, trihalomethyl, alkyloxy or alkylthio of 1 to 2 carbon atoms, halogen or a group of the formula $-NR^{10}R^{11}$, with the remaining substituent being hydrogen or methyl; or,

R^3, R^4 and R^5 are each hydrogen:

one of R^6, R^7 and R^8 is alkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, trihalomethyl hydroxyalkyl of l to 4 carbon atoms, alkyloxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkyloxycarbonylalkyl wherein the alkyl moieties each contain 1 to 2 carbon atoms, hydroxyl, alkyloxy or alkylthio of 1 to 4 carbon atoms, hydloxyalkyloxy of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkylsulfinyl or alkylsulfonyl of 1 to 4 carbon atoms, alkanoyl of 2 to 6 carbon atoms, alkoxycarbonyl wherein the alkyl moiety contains 1 to 3 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, a group of the formula $-NR^{12}-R^{13}$, halogen, cyano, nitro, azido or carboxyl, with the other two substituents being hydrogen; or, two of R^6, R^7 and R^8 are independently alkyl of l to 2 carbon atoms, trihalomethyl, alkyloxy or alkylthio 1 to 2 carbon atoms, halogen or a group of the formula $-NR^{12}R^{13}$, with the remaining substituent being hydrogen; or,

R^6, R^7 and R^8 are each hydrogen; and,

R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, alkyl of 1 to 4 carbon atoms, alkenylmethyl of alkynylmethyl of 2 to 4 carbon atoms, aryl or arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by methyl, methoxy or halogen), mono- or dihydroxyalkylmethyl of 2 to 4 carbon atoms, alkyoxy of 1 to 3 carbon atoms, hydroxy, alkyloxyethyl or alkylthioethyl of 3 to 4 carbon atoms, aminoalkylmethyl of 2 to 4 carbon atoms, mono- or dialkylaminoalkylmethyl wherein each alkyl moiety contains 1 or 2 carbon atoms, or alkanoyl of 1 to 4 carbon atoms; or,

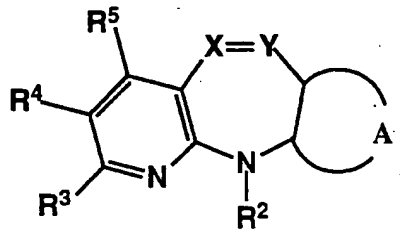
R^{10} and R^{11}, and R^{12} and R^{13}, together with the nitrogen atoms between them, respectively and independently form azetidin-1-yl or a 5, 6 or 7-membered

ring which is either saturated or unsaturated, which optionally contains up to one additional heteroatom which may be selected from O, S or N, or which optionally contains in place of a carbon atom a group of the formula $=NR^{14}$ wherein R^{14} is hydrogen or alkyl or 1 to 2 carbon atoms, and which ring is optionally and independently substituted with hydroxymethyl, aminomethyl, 1 to 4 methyl groups and 1 to 2 hydroxy groups; subject to the proviso that when

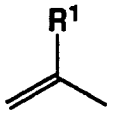
a) Z is oxygen or sulphur

b) R^2 is hydrogen, alkyl of 1 to 5 carbon atoms, alkenyl or alkinyl of 2 to 5 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 2 to 4 carbon atoms, hydroxyalkyl of 2 to 5 carbon atoms, phenyl (optionally substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), or alkoxycarbonylmethyl wherein the alkyl moiety contains 1 to 5 carbon atoms.

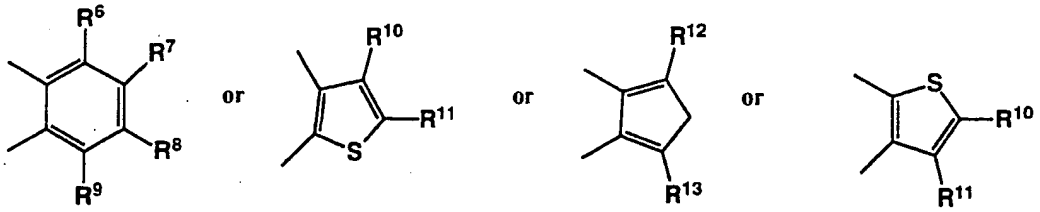
BOEHRINGER 7 refers to the compounds of claim 1 of European Publication 498 290 A1, compounds of the formula



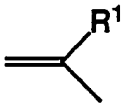
wherein, one of X and Y is -N = and the other is



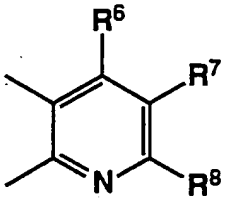
where A is a fused ring of the formula



or, when X is -N = and Y is



A may additionally be



R^1 is cyano, chloro, bromo, imidazolyl, phosphetanyl, phospholanyl, or phosphorinanyl, or a group of the formula $-OR^{14}$, $-SR^{14}$, $-SOR^{14}$, $-SO_2R^{14}$, $-NH_2$, $-NHR^{14}$, $-NR^{14}R^1$ $-PR^{14}R^{15}$, $-P(OR^{14})(OR^{15})$, $-P(O)(OR^{15})(OR^{15})$, $-P0_3H_2$, $-P(NR^{14}R^{15})(NR^{14})(R^{15})$, or $-P(O)(NR^{14}R^{15})(NR^{14}R^{15})$, wherein R^{14} and R^{15} are each independently alkyl of 1 to 4 carbon atoms, which may optionally be substituted by a cyano or alkoxycarbonyl group of 2 to 4 carbon atoms, cyclopropyl or cyclobutyl, or the group $-NR^{14}R^{15}$ may be pyrrolidine, piperidine, or morpholine;

R^2 is hydrogen, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 6 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 5 carbon atoms, alkanoyl of 2 to 5 carbon atoms, hydroxyalkyl of 2 to 6 carbon atoms, aryl or arylmethyl (wherein aryl means thiazolyl, oxazolyl or isoxazol, which is unsubstituted, or is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or

halogen), alkoxycarbonylmethyl wherein the alkoxy moiety contains 1 to 5 carbon atoms, oxetanyl, thietanyl, tetrahydrothienyl, tetrahydrofuranyl, cyano;

R^3, R^4 and R^5 are each independently hydrogen, alkyl of 1 to 3 carbon atoms or chloro, with the proviso that at least one of these substituents is hydrogen or methyl; or

one of R^3, R^4 and R^5 is alkyl of 1 to 6 carbon atoms, alkanoyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, alkenyl or alkynyl of 2 to 6 carbon atoms, hydroxyalkyl of 1 to 6 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 5 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, halogen, trihalomethyl, hydroxyl, alkoxy of 1 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, aryl or arylalkyl (wherein the alkyl moiety contains 1 to 3 carbon atoms, and the aryl moiety is phenyl, thienyl, furanyl, pyridyl, or imidazolyl, which is either unsubstituted or substituted by alkyl or alkoxy of 1 to 3 carbon atoms, hydroxyl or halogen), alkanoyl of 2 to 6 carbon atoms, alkoxycarbonyl wherein the alkyl moiety contains 1 to 3 carbon atoms, hydroxyalkoxy of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkylsulfinyl or alkylsulfonyl of 1 to 4 carbon atoms, alkanoylamino of 1 to 3 carbon atoms, aminoalkyl of 1 to 4 carbon atoms, mono- or di-alkylamino or mono- or di-alkylaminocarbonyl, wherein each alkyl moiety contains 1 to 3 carbon atoms, a group of the formula $-NR^{16}R^{17}$, N-pyrrolidino, N-piperidino, N-morpholino, carboxyalkyl of 2 to 3 carbon atoms, cyano, nitro, carboxyl, carbamyl, amino, azido, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 3 carbon atoms, with the proviso that the remaining two substituents are hydrogen, methyl or chloro; or

two of R^3, R^4 and R^5 are independently alkyl or hydroxyalkyl of 1 to 2 carbon atoms, trihalomethyl, alkyloxy or alkylthio of 1 to 2 carbon atoms, halogen or a group of the formula $NR^{16}R^{17}$, with the remaining substituent being hydrogen, methyl or chloro;

R^6 R^7, R^8 and R^9 are each hydrogen; or

one of R^6, R^7, R^8 and R^9 is alkyl of 1 to 4 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms, alkoxyalkyl or alkylthioalkyl of 2 to 4 carbon atoms, alkanoyl of 1 to 6 carbon atoms, alkoxycarbonyl of 2 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, alkoxycarbonylalkyl wherein the alkoxy and alkyl moieties each contain 1 to 2 carbon atoms, halogen, trihalomethyl, hydroxyl, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, hydroxyalkyloxy of 2 to 4 carbon atoms, alkanoyloxy of 2 to 4 carbon atoms, alkylsulfinyl or alkylsulfonyl of 1 to 4

carbon atoms, alkanoylamino of 1 to 3 carbon atoms, aminoalkyl of 1 to 3 carbon atoms, mono- or di-alkylamino or mono or di-alkylaminocarbonyl wherein each alkyl moiety contains 1 to 2 carbon atoms, carboxyalkyl of 2 to 3 carbon atoms, halogen, cyano, nitro, carboxyl, carbamyl, amino, azido, aminoalkyl of 1 to 4 carbon atoms, mono- or di-alkylaminoalkyl wherein each alkyl moiety contains 1 to 2 carbon atoms, a group of the formula $-NR^{18}R^{19}$, and the remaining two or three substituents are hydrogen or two of the remaining three substitutents are hydrogen and one is methyl, ethyl or halogen;

when only R^6, R^7 and R^8 are present two of them are independently alkyl of 1 to 2 carbon atoms, trihalomethyl, alkyloxy or alkylthio of 1 to 2 carbon atoms, halogen, or a group of the formula $-NR^{18}R^{19}$, with the remaining substituent being hydrogen;

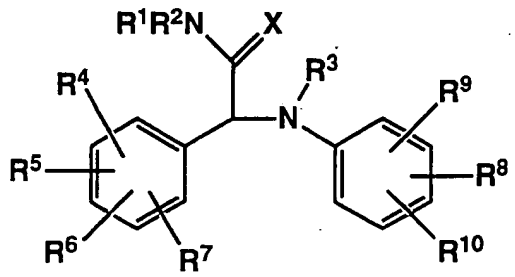
R^{10} and R^{11} are chosen from hydrogen, alkyl of 1 to 4 carbon atoms, halogen, cyano, nitro and alkanoyl of 1 to 3 carbon atoms, and

R^{12} and R^{13} are each independently hydrogen, alkyl of 1 to 4 carbon atoms, halogen or nitro;

R^{16}, R^{17}, R^{18} and R^{19} are each independently hydrogen, alkyl of 1 to 4 carbon atoms, alkenylmethyl or alkynylmethyl of 2 to 4 carbon atoms, aryl or arylmethyl (wherein the aryl moiety is phenyl, thienyl or furanyl, which is either unsubstituted or substituted by methyl, methoxy or halogen), mono- or di-hydroxyalkylmethyl of 2 to 4 carbon atoms, alkyloxy of 1 to 3 carbon atoms, hydroxy, alkyloxyethyl or alkylthioethyl of 3 to 4 carbon atoms, aminoalkylmethyl of 1 to 4 carbon atoms, mono- or dialkylaminoalkyl-methyl wherein each alkyl moiety contains 1 to 2 carbon atoms, or alkanoyl of 1 to 4 carbon atoms; or R^{16}, R^{17}, R^{18} and R^{19}, together with the nitrogen atoms between them, respectively and independently from azetidin-1-yl or a 5, 6, or 7-membered ring which is either saturated or unsaturated, which optionally contains up to one additional heteroatom which may be selected from O, S or N, or which optionally contains in place of a carbon atom a group of the formula $=NR^{20}$ wherein R^{20} is hydrogen or alkyl of 1 to 2 carbon atoms, and which ring is optionally independently substituted with hydroxymethyl, aminomethyl, 1 to 4 methyl groups and 1 to 2 hydroxy groups; or a pharmaceutically acceptable acid addition salt thereof.

BOEHRINGER COMPOUNDS refers to the compounds of BOEHRINGER 1, BOEHRINGER 2, BOEHRINGER 3, ... BOEHRINGER 7.

JANSSEN 1 refers to the compounds of claim 1 of International Public No. WO 92/00952, HIV-inhibiting benzeneacetamides of the formula:



a pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof, wherein

R^1 and R^2 each independently are hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl; or

R^1 and R^2 taken together with the nitrogen atom bearing said R^1 and R^2 may form a pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl or 4-C_{1-4}alkylpiperazinyl group;

X is O or S;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 R^5 and R^6 each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, trifluoromethyl, cyano, aminomethyl, carboxyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, aminocarbonyl or hydroxy;

R^7 is hydrogen or halo; and

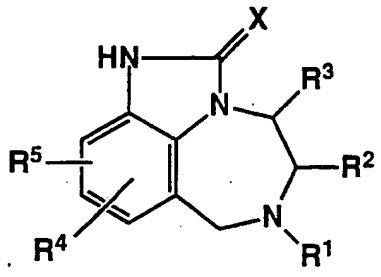
R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro, hydroxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, (trifluoromethyl)carbonyl, aminocarbonyl, (cyclopropyl)carbonyl or a radical C_{1-6}alkyl-(C=Y)- wherein = Y represents =O, =N-OH, =N-OCH_3, =N-NH_2 or =N-$N(CH_3)_2$;

provided that:

(1) R^1 is other than n-propyl when R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} represent hydrogen, R^8 represents 4-ethoxy and X represents oxygen, and

(2) X is other than sulfur, when R^1, R^2, R^3, R^6, R^7, R^8, R^9 and R^{10} represent hydrogen and R^4 and R^5 represent 3,4-dimethoxy.

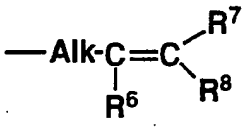
JANSSEN 2 refers to the compounds of claim 1 of International Public No. WO 92/00979, antiviral tetrahydroimidazo[1,4]benzodiazeepin-2-(thio)ones of the formula:

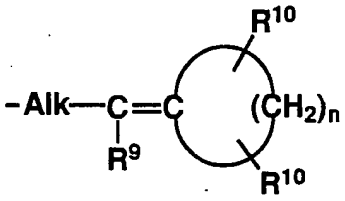


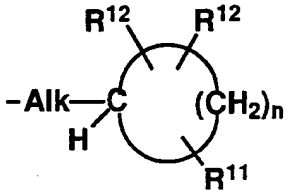
a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

X is O or S;

R^1 is a radical of formula:

 (a-1);



 (a-3) or

Alk is C_{1-6}alkanediyl;

R^6 is hydrogen, halo or C_{1-4}alkyl;

R^7 and R^8 each independently are hydrogen, halo, C_{3-6}cycloalkyl, trifluoromethyl, 2,2,2-trifluoroethyl, C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy;

R^9 is hydrogen, halo or C_{1-4}alkyl;

each R^{10} independently is hydrogen or C_{1-4}alkyl; or both R^{10} taken together may form a C_{1-6}alkanediyl radical;

n is 2, 3, 4, 5 or 6;

R^{11} is hydrogen or C_{2-6}alkenyl;

each R^{12} independently is hydrogen or C_{1-4}alkyl; or both R^{12} taken together may form a C_{1-6}alkanediyl radical;

m is O, 1 or 2;

R^{13} is C_{1-6}alkyl, aryl, arylmethyl, C_{3-6}cycloalkyl or (C_{3-6}cycloalkyl) C_{1-4}alkyl;

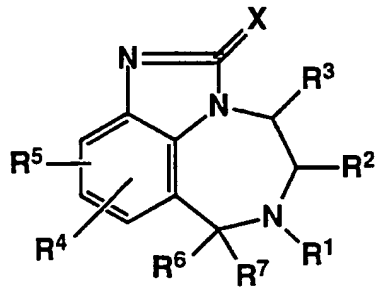
R^2 is hydrogen or C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 each independently are hydrogen, C_{1-6}alkyl, halo, cyano, nitro, trifluoromethyl, hydroxy, C_{1-6}alkyloxy, amino, mono- or di(C_{1-6} alkyl)amino, C_{1-6}alkylcarbonylamino or arylcarbonylamino; and each aryl is phenyl optionally substituted with from 1 to 3 substituents independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, amino, nitro and trifluoromethyl;

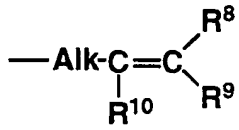
provided that when R^4 or R^5 is other than C_{1-6}alkylcarbonylamino or arylcarbonylamino, then R^1 is other than C_{3-6}alkenyl and (C_{3-6}cycloalkyl)C_{1-6}alkyl.

JANSSEN 3 refers to the compounds of claim 1 of European Patent Publication No. 417 840 A1, antiviral tetrahydroimidazo[1,4]-benzodiazepines of the formula:

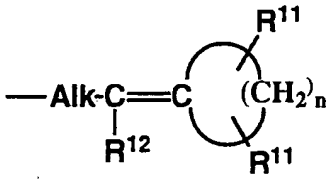


a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

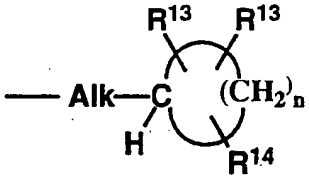
R^1 is C_{1-6}alkyl optionally substituted with aryl; C_{3-6}alkynyl; C_{3-6}cycloalkyl; or a radical of formula:



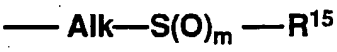
(a-1);



(a-2);



(a-3); or



(a-4);

Alk is C_{1-6}alkanediyl;

R^8 and R^9 each independently are hydrogen, halo, C_{3-6}cycloalkyl, trifluoromethyl, 2,2,2-trifluoroethyl, C_{1-4}alkyl optionally substituted with C_{1-4} alkyloxy;

R^{10} is hydrogen, halo or C_{1-4}alkyl;

each R^{11} independently is hydrogen or C_{1-4}alkyl; or both R^{11} taken together may form a C_{1-6}alkanediyl radical;

R^{12} is hydrogen, halo or C_{1-4}alkyl;

n is 2, 3, 4, 5 or 6;

each R^{13} independently is hydrogen or C_{1-4}alkyl; or both R^{13} taken together may form a C_{1-6}alkanediyl radical;

R^{14} is hydrogen or C_{2-6}alkenyl;

m is 0, 1 or 2;

R^{15} is C_{1-6}alkyl, aryl, arylmethyl, C_{3-6}cycloalkyl or (C_{3-5} cycloalkyl)C_{1-6}alkyl;

R^2 is hydrogen or C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 each independently are hydrogen, C_{1-6}alkyl, halo, cyano, nitro, trifluoromethyl, hydroxy, C_{1-6}alkyloxy, amino, mono or di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylamino or arylcarbonylamino; R^6 is C_{1-6}alkyl;

R^7 is hydrogen or C_{1-6}alkyl;

X is OH, SH or $NR^{16}R^{17}$;

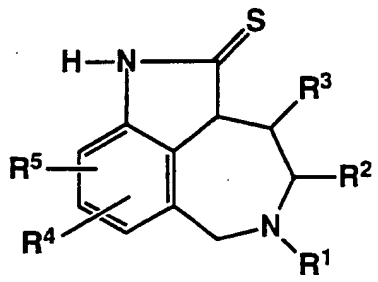
R^{16} is hydrogen, C_{1-6}alkyl, aryl, cyano, hydroxy, amino, nitro, C_{1-}

$_6$alkyloxycarbonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl or arylsulfonyl;

R^{17} is hydrogen, C_{1-6}alkyl or aryl; and

each aryl is phenyl optionally substituted with from 1 to 3 substituents independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, amino, nitro and trifluoromethyl.

JANSSEN 4 refers to the compounds of claim 1 of European Patent Publication No. 384 522 A1, antiviral tetrahydroimidazo[1,4]-benzodiazepin-2-thiones of the formula:



a pharmaceutically acceptable acid salt or a stereochemically isomeric form thereof, wherein

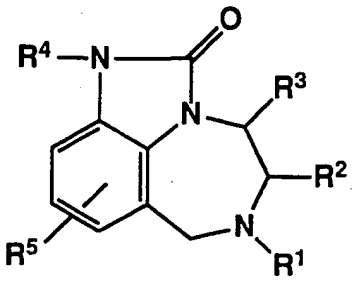
R^1 is C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, or C_{1-6}alkyl substituted with aryl or with C_{3-6}cycloalkyl;

R^2 is hydrogen or C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 each independently are hydrogen, C_{1-6}alkyl, halo, cyano, nitro, trifluoromethyl, hydroxy, C_{1-6}alkyloxy, amino or mono-or di(C_{1-6}alkylamino); and aryl is phenyl optionally substituted with from 1 to 3 substituents independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, amino, nitro and trifluoromethyl.

JANSSEN 5 refers to the compounds of claim 1 of European Patent Publication No. 336 466 A1, antiviral tetrahydroimidazo[1,4]-benzodiazepin-2-ones of the formula



a pharmaceutically acceptable acid addition salt or a stereochemically isomeric forms thereof, wherein

R^1 is hydrogen, C_{1-8}alkyl, C_{3-6}alkenyl, C_{1-6}-alkynyl, C_{1-6}alkylcarbonyl, C_{1-4}cycloalkyl, or substituted with aryl, hydroxy, cyano or C_{3-6}cycloalkyl;

R^2 is hydrogen, C_{1-6}alkyl or C_{3-6}alkenyl;

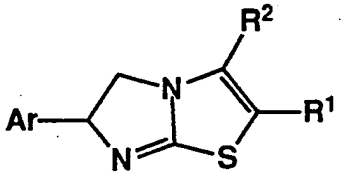
R^3 is hydrogen, or C_{1-6}alkyl;

R^4 is hydrogen, C_{1-6}alkyl optionally substituted with hydroxy, cyano, hydroxycarbonyl or carbonyl C_{1-6}alkylcarbonyl; C_{3-6}alkenyl; C_{3-6}cycloalkyl; C_{5-6}cycloalkenyl;

R^5 is hydrogen, C_{1-6}alkyl or halo; and

aryl is phenyl optionally substituted with up to 3 substituents independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkyloxy, amino, nitro and trifluoromethyl.

JANSSEN 6 refers to the compounds of claim 1 of European Patent Publication No. 430 334 A1, immunostimulating 6-aryl-5,6-dihydroimidazo[2,1-b]thiazoles of the formula:



a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein

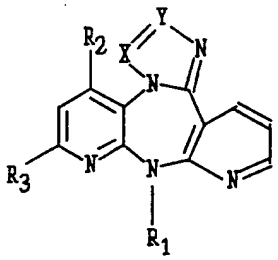
Ar is phenyl optionally substituted with from 1 to 3 substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, mercapto, C_{1-6}alkylthio, C_{1-6}alkyl, nitro, amino, mono, and di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylamino, arylcarbonylamino, C_{1-6}alkylsulfonylamino, trifluoromethyl, cyano, aminocarbonyl, mono- and di(C_{1-6}alkyl)aminocarbonyl, hydroxycarbonyl, C_{1-6}alkyloxyamino,

carboxaldehyde and hydroxymethyl; pyridinyl; thienyl, furanyl or furanyl substituted with either C_{1-6}alkyl or halo;

R^1 and R^2 each independently are C_{1-20}alkyl, (C_{3-7}cycloalkyl), C_{1-5}alkyl, C_{3-7}cycloalkyl, aryl or (aryl)-C_{1-6}alkyl; and one of R^1 and R^2 may also be hydrogen; or R^1 and R^2 taken together may also form a C_{3-6}alkanediyl radical; each aryl independently is phenyl optionally substituted with from 1 to 3 substituents each independently selected from halo, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyl, nitro, amino, trifluoromethyl or cyano.

JANSSEN COMPOUNDS refers to the compounds of JANSSEN 1, JANSSEN 2, JANSSEN 3, ... JANSSEN 6.

PFIZER 1 refers to the compounds of the formula



where X and Y are the same or different and are -N=, -CR_4= where R_4 is -H or -CH_3;

where R_1 is C_1-C_3 alkyl or cyclopropyl;

where R_2 is -H or -CH_3;

where R_3 is -H or -OR_{3-1} where R_{3-1} is C_1-C_3 alkyl, -$N(R_{3-2})(R_{3-3})$ where R_{3-2} and R_{3-3} are the same or different and are -H or C_1-C_4 alkyl.

PFIZER COMPOUNDS refers to the compounds of PFIZER 1.

NON-NUCLEOSIDE HIV TREATMENT DRUG refers to MERCK COMPOUNDS + BOEHRINGER COMPOUNDS + JANSSEN COMPOUNDS + PFIZER COMPOUNDS.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and

techniques.

EXAMPLE 1 SENSITIZING HIV-1 INHIBITOR Followed By NON-NUCLEOSIDE HIV TREATMENT DRUG

A 21 year old male, HIV positive patient with no symptoms is treated by administering 500 mg of 1-[2-(5-methoxyindolyl)carbonyl]-4-[3-(N-ethylamino)-2-pyridinyl)piperazine orally three times daily for 3 months. The patients blood is monitored to insure that a sustainable blood level is achieved which is above the MIC of the HIV virus. This initial sensitizing course is followed by 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one (BI-RG-587, nevirapine) administered orally in a dose of 200 mg once a day.

EXAMPLE 2 SENSITIZING HIV-1 INHIBITOR Followed By NON-NUCLEOSIDE HIV TREATMENT DRUG

A 45 year old female, HIV positive who is symptomatic is treated with 1-[2-(5-methanesulfonamidoindolyl)carbonyl]-4-[3-(N-isopropylamino)-2-pyridinyl]piperazine, 50 mg orally three times daily for a period of 8 weeks, followed by 3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one which is administered orally 250 mg three times daily.

EXAMPLE 3 SENSITIZING HIV-1 INHIBITOR Followed By NON-NUCLEOSIDE HIV TREATMENT DRUG

A 2 month old child who is HIV positive with no symptoms is treated with 1-[2-(5-methoxyindolyl)carbonyl]-4-[3-(N-ethylamino)-2-pyridinyl)piperazine, 1 mg/kg orally four times daily for a period of 3 months followed by (+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione, 50 mg intravenously continuously daily.

EXAMPLE 4 SENSITIZING HIV-1 INHIBITOR Concurrently With NON-NUCLEOSIDE HIV TREATMENT DRUG

A 29 year old female, HIV positive with no symptoms is treated with 1-[2-(5-methoxyindolyl)carbonyl]-4-[3-(N-ethylamino)-2-pyridinyl)piperazine, 400 mg by mouth four times daily for 2 months concurrently with 3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one given 500 mg orally twice daily indefinitely.

EXAMPLE 5 SENSITIZING HIV-1 INHIBITOR Concurrently With NON-NUCLEOSIDE HIV TREATMENT DRUG

A 17 year old male, symptomatic with HIV, is treated concurrently with 1-[2-(5-methanesulfonamidoindolyl)carbonyl]-4-[3-(N-isopropylamino)-2-pyridinyl]-piperazine, 150 mg by mouth every 8 hours, concurrent with 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one, 400 mg by mouth

daily.

EXAMPLE 6 SENSITIZING HIV-1 INHIBITOR Concurrently With NON-NUCLEOSIDE HIV TREATMENT DRUG

A 6 year old child symptomatic with HIV, is treated with 1-[2-(5-methanesulfonamidoindolyl)carbonyl]-4-[3-(N-isopropylamino)-2-pyridinyl]piperazine at a dose of 0.5 mg/kg, four times daily concurrently with (-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide, 150 mg orally three times daily.

CLAIMS

1. Use of a NON-NUCLEOSIDE HIV TREATMENT DRUG to prepare a medicament for treatment of HIV positive individuals having strains of HIV showing increased sensivity thereto due to the administration of a SENSITIZING HIV-1 INHIBITOR.

2. Use according to claim 1 where the SENSITIZING HIV-1 INHIBITOR is selected from the group consisting of BHAP COMPOUNDS.

3. Use according to claim 2 where the where the BHAP COMPOUND is

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]-piperazine and

1-[5-methanesulfonamidoindolyl-2-carbonyl]-4-[3-(1-methylethyl-amino)-2-pyridinyl]piperazine.

4. Use according to claim 1 where the sensitizingly effective amount of the SENSITIZING HIV-1 INHIBITOR is from about 50 to about 3,000 mg per day.

5. Use according to claim 1 where more than one SENSITIZING HIV-1 INHIBITOR is used.

6. Use according to claim 1 where more than one NON-NUCLEOSIDE HIV TREATMENT DRUG is used.

7. Use according to claim 1 where the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured by clinical resistance to the SENSITIZING HIV-1 INHIBITOR.

8. Use according to claim 1 where the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured *in vitro* by an increase in p24 antigen.

9. Use according to claim 1 where the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured *in vitro* by a measurement which detects a change in the amino acid 236 of the reverse transcriptase.

10. Use according to claim 1 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is selected from the group consisting of MERCK COMPOUNDS, BOEHRINGER COMPOUNDS, JANSSEN COMPOUNDS and PFIZER COMPOUNDS.

11. Use according to claim 10 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of MERCK COMPOUNDS.

12. Use according to claim 11 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a MERCK COMPOUND selected from the group consisting of

3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-{[(4,7-Dimethyl-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one,

5-ethyl-6-methyl-3-(2-phthalimidoethyl)pyridin-2(1H)-one,

3-{[1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-pyridin-2(1H)-one.

13. Use according to claim 10 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of BOEHRINGER COMPOUNDS.

14. Use according to claim 13 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one.

15. Use according to claim 10 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of JANSSEN COMPOUNDS.

16. Use according to claim 15 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a JANSSEN COMPOUND selected from the group consisting of

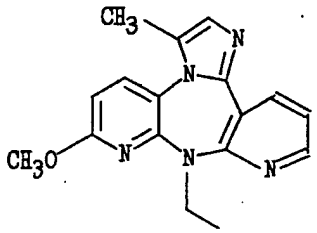
(+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,l-jk][1,4]benzodiazepin-2(1H)-thione,

(+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,l-jk][1,4]benzodiazepin-2(1H)-thione,

(-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,
(-)-α-[(5-methyl-2nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,
(-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide,
(-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide,
α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide,
α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,
α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide.

17. Use according to claim 10 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of PFIZER COMPOUNDS.

18. Use according to claim 17 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is



19. Use according to claim 1 where an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG is from about 50 to about 4,000 mg per day.

20. Use according to claim 1 where administration of the NON-NUCLEOSIDE HIV TREATMENT DRUG follows administration of the SENSITIZING HIV-1 INHIBITOR.

21. Use according to claim 1 where where after the initial administration of the SENSITIZING HIV-1 INHIBITOR, the NON-NUCLEOSIDE HIV TREATMENT DRUG is administered concurrently with the SENSITIZING HIV-1 INHIBITOR.

22. Use according to claim 1 where after the initial administration of the SENSITIZING HIV-1 INHIBITOR, the NON-NUCLEOSIDE HIV TREATMENT DRUG is administered intermittently with the SENSITIZING HIV-1 INHIBITOR.

23. Use of a NON-NUCLEOSIDE HIV TREATMENT DRUG to prepare a medicament for the treatment of HIV positive individuals concurrently receiving a SENSITIZING HIV-1 INHIBITOR.

24. Use according to claim 23 where the SENSITIZING HIV-1 INHIBITOR is selected from the group consisting of BHAP COMPOUNDS.

25. Use according to claim 23 where the BHAP COMPOUND is

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]-piperazine and

1-[5-methanesulfonamidoindolyl-2-carbonyl]-4-[3-(1-methylethyl-amino)-2-pyridinyl]piperazine.

26. Use according to claim 23 where the sensitizingly effective amount of the SENSITIZING HIV-1 INHIBITOR is from about 50 to about 3,000 mg per day.

27. Use according to claim 23 where more than one SENSITIZING HIV-1 INHIBITOR is used.

28. Use according to claim 23 where more than one NON-NUCLEOSIDE HIV TREATMENT DRUG is used.

29. Use according to claim 23 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is selected from the group consisting of MERCK COMPOUNDS, BOEHRINGER COMPOUNDS, JANSSEN COMPOUNDS and PFIZER COMPOUNDS.

30. Use according to claim 23 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of MERCK COMPOUNDS.

31. Use according to claim 30 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a MERCK COMPOUND selected from the group consisting of

3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-{[(4,7-Dimethyl-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one,

5-ethyl-6-methyl-3-(2-phthalimidoethyl)pyridin-2(1H)-one,

3-{[1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-pyridin-2(1H)-one.

32. Use according to claim 23 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of BOEHRINGER COMPOUNDS.

33. Use according to claim 32 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one.

34. Use according to claim 23 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of JANSSEN COMPOUNDS.

35. Use according to claim 34 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a JANSSEN COMPOUND selected from the group consisting of

(+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,l-jk][1,4]benzodiazepin-2(1H)-thione,

(+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,l-jk][1,4]benzodiazepin-2(1H)-thione,

(-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(5-methyl-2nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide,

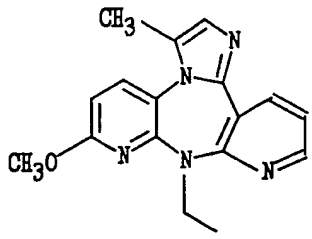
α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide.

36. Use according to claim 23 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of PFIZER COMPOUNDS.

37. Use according to claim 36 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is



38. Use according to claim 23 where an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG is from about 50 to about 4,000 mg per day.

39. Use according to claim 23 where after the initial concurrent administration of the SENSITIZING HIV-1 INHIBITOR and the NON-NUCLEOSIDE HIV TREATMENT DRUG, the concurrent administration of the SENSITIZING HIV-1 INHIBITOR and the NON-NUCLEOSIDE HIV TREATMENT DRUG is continued.

40. Use according to claim 23 where after the initial concurrent administration of the SENSITIZING HIV-1 INHIBITOR and INHIBITOR and the NON-NUCLEOSIDE HIV TREATMENT DRUG are administered intermittently.

41. A method of treating a HIV positive human which comprises

(1) administering to the HIV positive individual a sensitizingly effective amount of a SENSITIZING HIV-1 INHIBITOR until increased sensitivity to a NON-NUCLEOSIDE HIV TREATMENT DRUG develops,

(2) administering to the HIV-positive individual an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG.

42. A method of treating a HIV positive human according to claim 41 where the SENSITIZING HIV-1 INHIBITOR is selected from the group consisting of BHAP COMPOUNDS.

43. A method of treating a HIV positive human according to claim 42 where the BHAP COMPOUND is

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]-piperazine and

1-[5-methanesulfonamidoindolyl-2-carbonyl]-4-[3-(1-methylethyl-amino)-2-pyridinyl]piperazine.

44. A method of treating a HIV positive human according to claim 41 where the sensitizingly effective amount of the SENSITIZING HIV-1 INHIBITOR is from about 50 to about 3,000 mg per day.

45. A method of treating a HIV positive human according to claim 41 where more than one SENSITIZING HIV-1 INHIBITOR is used.

46. A method of treating a HIV positive human according to claim 41 where more than one NON-NUCLEOSIDE HIV TREATMENT DRUG is used.

47. A method of treating a HIV positive human according to claim 41 where the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured by clinical resistance to the SENSITIZING HIV-1 INHIBITOR.

48. A method of treating a HIV positive human according to claim 41 where the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured *in vitro* by an increase in p24 antigen.

49. A method of treating a HIV positive human according to claim 41 where the increased sensitivity to the NON-NUCLEOSIDE HIV TREATMENT DRUG is measured *in vitro* by a measurement which detects a change in the amino acid 236 of the reverse transcriptase.

50. A method of treating a HIV positive human according to claim 41 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is selected from the group consisting of MERCK COMPOUNDS, BOEHRINGER COMPOUNDS, JANSSEN COMPOUNDS and PFIZER COMPOUNDS.

51. A method of treating a HIV positive human according to claim 50 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of MERCK COMPOUNDS.

52. A method of treating a HIV positive human according to claim 51 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a MERCK COMPOUND selected from the group consisting of

3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-{[(4,7-Dimethyl-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one,

5-ethyl-6-methyl-3-(2-phthalimidoethyl)pyridin-2(1H)-one,

3-{[1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-pyridin-2(1H)-one.

53. A method of treating a HIV positive human according to claim 50 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of BOEHRINGER COMPOUNDS.

54. A method of treating a HIV positive human according to claim 53 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one.

55. A method of treating a HIV positive human according to claim 50 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of JANSSEN COMPOUNDS.

56. A method of treating a HIV positive human according to claim 55 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a JANSSEN COMPOUND selected from the group consisting of

(+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,l-jk][1,4]benzodiazepin-2(1H)-thione,

(+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,l-jk][1,4]benzodiazepin-2(1H)-thione,

(-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(5-methyl-2nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide,

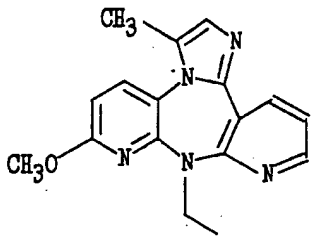
α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide.

57. A method of treating a HIV positive human according to claim 50 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of PFIZER COMPOUNDS.

58. A method of treating a HIV positive human according to claim 57 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is



59. A method of treating a HIV positive human according to claim 41 where an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG is from about 50 to about 4,000 mg per day.

60. A method of treating a HIV positive human according to claim 41 where administration of the NON-NUCLEOSIDE HIV TREATMENT DRUG follows administration of the SENSITIZING HIV-1 INHIBITOR.

61. A method of treating a HIV positive human according to claim 41 where after the initial administration of the SENSITIZING HIV-1 INHIBITOR, the NON-NUCLEOSIDE HIV TREATMENT DRUG is administered concurrently with the SENSITIZING HIV-1 INHIBITOR.

62. A method of treating a HIV positive human according to claim 41 where after the initial administration of the SENSITIZING HIV-1 INHIBITOR, the NON-NUCLEOSIDE HIV TREATMENT DRUG is administered intermittently with the SENSITIZING HIV-1 INHIBITOR.

63. A method of treating a HIV positive human which comprises administering to the HIV positive individual a sensitizingly effective amount of one or more SENSITIZING HIV-1 INHIBITOR concurrently with an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG.

64. A method of treating a HIV positive human according to claim 63 where the SENSITIZING HIV-1 INHIBITOR is selected from the group consisting of BHAP COMPOUNDS.

65. A method of treating a HIV positive human according to claim 63 where the BHAP COMPOUND is

1-[5-methoxyindolyl-2-carbonyl]-4-[3-(ethylamino)-2-pyridinyl]-piperazine and

1-[5-methanesulfonamidoindolyl-2-carbonyl]-4-[3-(1-methylethyl-amino)-2-pyridinyl]piperazine.

66. A method of treating a HIV positive human according to claim 63 where the sensitizingly effective amount of the SENSITIZING HIV-1 INHIBITOR is from about 50 to about 3,000 mg per day.

67. A method of treating a HIV positive human according to claim 63 where more than one SENSITIZING HIV-1 INHIBITOR is used.

68. A method of treating a HIV positive human according to claim 63 where more than one NON-NUCLEOSIDE HIV TREATMENT DRUG is used.

69. A method of treating a HIV positive human according to claim 63 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is selected from the group consisting of MERCK COMPOUNDS, BOEHRINGER COMPOUNDS, JANSSEN COMPOUNDS and PFIZER COMPOUNDS.

70. A method of treating a HIV positive human according to claim 63 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of MERCK COMPOUNDS.

71. A method of treating a HIV positive human according to claim 70 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a MERCK COMPOUND selected from the group consisting of

3-{[(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-{[(4,7-Dimethyl-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one,

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one,

5-ethyl-6-methyl-3-(2-phthalimidoethyl)pyridin-2(1H)-one,

3-{[1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methyl-pyridin-2(1H)-one.

72. A method of treating a HIV positive human according to claim 63 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of BOEHRINGER COMPOUNDS.

73. A method of treating a HIV positive human according to claim 72 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is 6,11-dihydro-11-cyclopropyl-4-methyldipyrido[2,3-b:2',3'-e]-[1,4]diazepin-6-one.

74. A method of treating a HIV positive human according to claim 63 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of JANSSEN COMPOUNDS.

75. A method of treating a HIV positive human according to claim 74 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a JANSSEN COMPOUND selected from the group consisting of

(+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione,

(+)-(5S)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione,

(-)-α-[(2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(5-methyl-2nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetylphenyl)amino]-2,6-dichlorobenzeneacetamide,

(-)-α-[(2-acetyl-5-methylphenyl)amino]-2,6-dichlorobenzeneacetamide,

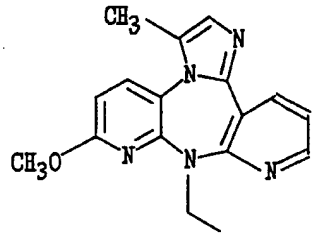
α-[(2-acetyl-5-chlorophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(5-chloro-2-nitrophenyl)amino]-2,6-dichlorobenzeneacetamide,

α-[(2-acetyl-5-fluorophenyl)amino]-2,6-dichlorobenzeneacetamide.

76. A method of treating a HIV positive human according to claim 63 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is a compound selected from the group consisting of PFIZER COMPOUNDS.

77. A method of treating a HIV positive human according to claim 76 where the NON-NUCLEOSIDE HIV TREATMENT DRUG is



78. A method of treating a HIV positive human according to claim 63 where an effective amount of a NON-NUCLEOSIDE HIV TREATMENT DRUG is from about 50 to about 4,000 mg per day.

79. A method of treating a HIV positive human according to claim 63 where after the initial concurrent administration of the SENSITIZING HIV-1 INHIBITOR and the NON-NUCLEOSIDE HIV TREATMENT DRUG, the concurrent administration of the SENSITIZING HIV-1 INHIBITOR and the NON-NUCLEOSIDE HIV TREATMENT DRUG is continued.

80. A method of treating a HIV positive human according to claim 63 where after the initial concurrent administration of the SENSITIZING HIV-1 INHIBITOR and INHIBITOR and the NON-NUCLEOSIDE HIV TREATMENT DRUG are administered intermittently.

INTERNATIONAL SEARCH REPORT

Inter. ional Application No
PCT/US 93/08354

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/495 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOURNAL OF MEDICINAL CHEMISTRY vol. 36, no. 10 , 14 May 1993 pages 1505 - 1508 ROMERO, DONNA L. ET AL 'BIS(HETEROARYL)PIPERAZINE (BHAP) REVERSE TRANSCRIPTASE INHIBITORS: STRUCTURE-ACTIVITY RELATIONSHIPS OF NOVEL SUBSTITUTED INDOLE ANALOGUES AND THE IDENTIFICATION OF 1-((-METHANESULFONAMIDO-1H-INDOL-2-YL)-CARBONYL)-4-(3-((1-METHYL)AMINO)-PYRIDINYL)PIPERAZINE MONOMETHANESULFONATE (U-90152S), ETC.' see the whole document especially page 1507, column 1, line 49-column 2, line 19 --- -/--	1-14, 19-26, 29-33, 38-44, 47-54, 59-66, 69-73, 78-80

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1993	08. 12. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	MAIR, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VIROLOGY vol. 190, no. 1 , September 1992 pages 269 - 277 VASUDEVACHARI, M.B. ET AL 'PREVENTION OF THE SPREAD OF HIV-1 INFECTION WITH NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS' cited in the application see the whole document especially page 276, line11-15	1-80
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (USA) vol. 90, no. 10 , 15 May 1993 pages 4713 - 4717 DUEWEKE, T.J. ET AL 'A MUTATION IN REVERSE TRANSCRIPTASE OF BIS(HETEROARYL)PIPERAZINE-RESISTANT HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 THAT CONFERS INCREASED SENSITIVITY TO OTHER NONNUCLEOSIDE INHIBITORS' see the whole document	1-16, 19-35, 38-56, 59-75, 78-80
A	AIDS RESEARCH AND HUMAN RETROVIRUSES vol. 8, no. 5 , May 1992 pages 659 - 667 SARVER, N. ET AL 'FRONTIERS IN HIV-1 THERAPY: FOURTH CONFERENCE OF THE NIAID NATIONAL COOPERATIVE DRUG DISCOVERY GROUPS-HIV' see page 661, column 1, line 10 - column 2, line 50	1-80
P,X	JOURNAL OF VIROLOGY vol. 67, no. 9 , September 1993 pages 5353 - 5359 BALZARINI, JAN ET AL 'TREATMANT OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)-INFECTED CELLS WITH COMBINATIONS OF HIV-1-SPECIFIC INHIBITORS RESULTS IN A DIFFERENT RESISTANCE PATTERN THAN DOES TREATMENT WITH A SINGLE-DRUG THERAPY' see the whole document	1,2, 4-16, 19-24, 26-35, 38-42, 44-56, 59-64, 66-75, 78-80

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INTERNATIONAL SEARCH REPORT

Inte. ational application No.
PCT/US93/08354

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 41-80 are directed towards a method of treatment of the human body the search has been carried out and based upon the alleged effects of the compounds.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds which are theoretically defined by the Markish formulae of pages 12-54 of the description, the search has been mainly directed towards the specifically named compounds for economic reaso ns claims searched incompletely: 10,11,13,15,17,24,29,30,32,34,36,42,50, 51,53,55,57,64,69,70,72,74,76

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.